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RESTING-PULSE AND BLOOD-PRESSURE VALUES IN RELATION TO PHYSICAL FITNESS IN YOUNG MEN*

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IT IS customary to assume that the resting pulse of a normal adult man is about 70 beats per minute. The common belief is that when the resting pulse deviates much from this usual value, the heart is abnormal or there is functional disturbance of the circulatory mechanism associated with some medical condition such as infection or hyperthyroidism. Exception is made when one is dealing with well-trained athletes, whose resting pulse is usually lower than that of less trained or untrained persons. Resting pulses as low as 40 beats or even less have been observed in men who were accustomed to long and hard physical performances and who had been under fairly continuous training for periods of years.[1, 2] A high resting pulse is more often regarded as a pathologic sign, and pulses above 100 are considered so abnormal that, according to many physicians, a man whose cardiac rate remains persistently over 100 should be discarded from combat service in the Army or Navy. Cases have been called to our attention of outstanding athletes who have been rejected by examining boards because of high resting pulse.

Is the resting pulse an indication of the state of a man's physical fitness for hard muscular work? Data obtained in the course of general research in the Grant Study since 1938 help to clarify the problem. These data reveal a wide variability in normal young men that has not been sufficiently recognized.

The basis for this study was a series of measurements made on 265 college students selected without reference to athletic ability or physical fitness. For comparison, measurements were also made on a group of college athletes. The ages ranged from seventeen to twenty-two years. All the subjects had been previously declared normal after careful medical examination.

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PULSE AND BLOOD PRESSURE AT REST IN NORMAL YOUNG MEN

The basal pulse was counted in the morning, the subject being in the fasting state, after lying down for one hour for a basal-metabolism determination. The recumbent, sitting and standing pulse and blood pressure were taken during the course of the medical examination. The pulse and blood pressure were taken again while the subject was sitting for a period of at least ten minutes before a test on the treadmill. In this case the heart rate was recorded continuously by means of a Guillemin cardiotachometer, so that the subject did not know when his pulse was taken. The lowest reading obtained during this rest period was designated as the "sitting pulse before the treadmill."

Table 1 summarizes the findings on the college students. It is seen that under conditions of a routine and strictly private medical examination, performed by a physician who was known beforehand by the subjects, 6 men had a sitting pulse persistently above 100, and 12 men out of 253 had a systolic blood pressure persistently above 140 mm. It is also seen that the systolic blood pressure remained practically the same whether measured during the medical examination or before an experiment on the treadmill. On the other hand, the sitting pulse was definitely higher when taken before the treadmill test than during the medical examination.

PULSE AND BLOOD PRESSURE IN RELATION TO PHYSICAL FITNESS

An extensive study was made on 129 students and 18 varsity oarsmen in training. Their capacity to perform hard muscular work was measured. It included the following determinations: duration

of a run on a motor-driven treadmill at 7 miles per hour on an 8.6 per cent grade; blood pressure before and after work; pulmonary ventilation and oxygen consumption during the run; heart rate before, during and after work; and blood sugar as well as those between standing and lying pulses, also showed no relation to capacity to perform hard work. On the other hand, a close relation was found between performance capacity and rate of deceleration of the heart after work on the

TABLE 1. *Averages and Extremes of Pulse and Systolic Blood Pressure in Normal Young Men at Rest and before Muscular Exercise.*

MEASUREMENT	NO. OF CASES	AVERAGE	EXTREMES	REMARKS
Pulse:				
Basal	182	65	45–105	0.6% above 100
Recumbent (medical examination)	252	66	40–100	2.8% above 90
Sitting (medical examination)	252	73	48–105	6.3% above 90 and 2.4% above 100
Standing (medical examination)	194	82	54–124	12.4% above 100
Sitting (before treadmill walk)	127	84	50–124	14.7% above 100
Sitting* (before treadmill run)	231	90	55–136	26.4% above 100, including 6.1% above 110 and 3% above 120
Standing* (before treadmill run)	223	123	82–165	6.3% *below* 100
Systolic blood pressure:				
Recumbent	265	115	95–149	1.9% above 140 mm.
Sitting (medical examination)	253	123	100–155	4.7% above 140 mm.
Standing (medical examination)	194	121	90–174	7.7% above 140 mm.
Sitting (before treadmill test)	129	123	94–144	3.1% at 140 mm. and 0.8% above 140 mm.

*These measurements include college athletes.

and blood lactate after work. Taking into account these various factors, it was possible to determine how efficiently a man can perform exhausting work.[3–6] Accordingly, the subjects were divided into four categories in regard to their performing capacity: poor, average, good and excellent.

Among the students the average basal pulse was 65, with a range from 45 to 105. The average sitting pulse at the time of the medical examination was 73, with a range from 48 to 105. Before the treadmill test, the average sitting pulse increased to 84 with a range from 50 to 124, and 19 subjects had a sitting pulse persistently above 100. In respect to their ability to do hard work, 3 of the latter were poor, 14 average, and 2 good. The performance capacity of the remaining 110 men whose sitting pulse was below 100 was distributed in about the same range. The average sitting pulse of the oarsmen before training was 84, with a range from 50 to 116. These values compare closely with the findings on the students. After training, the average sitting pulse of the oarsmen dropped to 67 with a range from 50 to 82. All these men were good or excellent in ability to perform on the treadmill. Although the average pulse is lower in oarsmen when under training, the pulses of certain students were often as high as in untrained students who were much less fit.

With a few exceptions, no satisfactory relation was found between basal pulse or sitting pulse and capacity to perform hard work (Figs. 1 and 2). Differences between sitting and lying pulses,

treadmill up to exhaustion or to a maximum of five minutes. This relation has been described,[3–5] and the results of this study confirm the previous findings. Comparison of students with trained oarsmen shows that the average pulse of the stu-

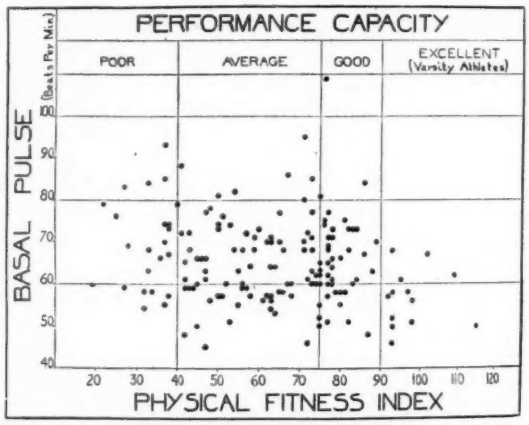

FIGURE 1. *Basal Pulse in Relation to Performance Capacity and Physical-Fitness Index.*

It should be noted that no significant relation exists between these measurements.

dents one minute after the run was 156, and of the oarsmen 130, whereas four minutes after the run the pulse was 114 for the students and 96 for the oarsmen. Individual pulses were regularly higher in the unfit subjects and lower in the fit (Fig. 3).

It is not commonly realized that in normal young men the maximum pulse during exhausting exercise may reach levels of 210 or more. In

the present series of 176 young men the maximum pulse (taken with the cardiotachometer) during the run ranged from 167 to 217 with an average of 193 (Fig. 4). For a run of the same duration the maximum pulse of trained subjects is usually lower than that of untrained subjects.

The average sitting systolic blood pressure was 123 mm. for the students with a range from 102 to 144. The average blood pressure was the same for the oarsmen with a range from 112 to 136. No satisfactory relation could be found between these measurements and the performance capacity of the students or the oarsmen (Fig. 5). The diastolic

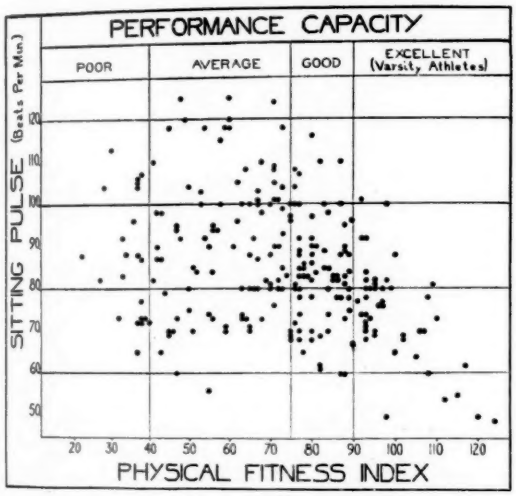

FIGURE 2. *Sitting Pulse in Relation to Performance Capacity and Physical-Fitness Index.*

It should be noted that, with the exception of 5 athletes who had pulses below 60 and at the same time a high index of fitness, no significant relation exists between these measurements.

blood pressure also showed no relation to the physical fitness of these men. No definite relation was established between physical fitness and differences between systolic blood pressure standing and lying, a factor that is a part of the Schneider test.

On the basis of these results and similar experiments performed at the Harvard Fatigue Laboratory, an index of physical fitness for hard muscular work was computed by taking into account the duration of the run on the treadmill and the rate of the heart deceleration during the first period of recovery. This method has been described[7] and has proved to yield valuable results in assessing that kind of fitness.[8, 9] The index is derived by dividing the duration of the run in seconds by the sum of three pulses counted at convenient intervals during the early recovery. The following interpretation is given to this index in the treadmill test: below 40, poor physical fitness; from 41 to 75, average; from 76 to 90, good; above 90, excellent.[7]

Figure 1 shows a lack of relation between the basal pulse and the physical-fitness index. Figure

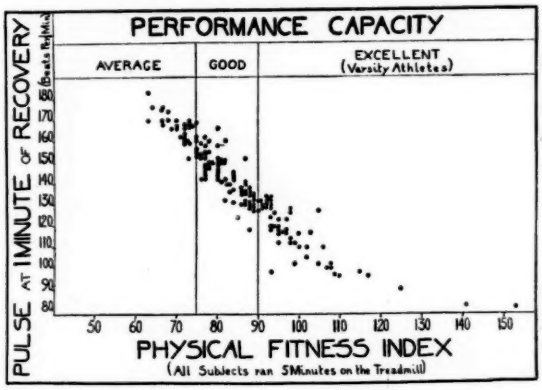

FIGURE 3. *Pulse after Exercise in Relation to Performance Capacity and Physical-Fitness Index.*

It should be noted that the men who were fittest had the lowest pulses in recovery.

2 shows a lack of relation between sitting pulse and the physical-fitness index, with the exception of 5 athletes who had a sitting pulse of 55 or below and a high fitness index. Pulses above 100 were found not only in the poor but also in the average and good groups, and even 2 varsity athletes had pulses of 100 and 102. Figure 3, on the contrary, shows a good relation between the pulse at one minute of recovery after the treadmill run and the performance capacity and the fitness

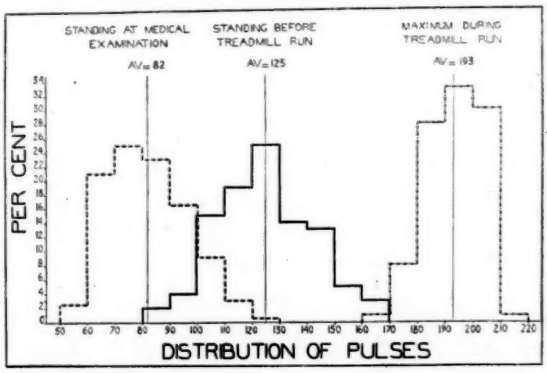

FIGURE 4. *Distribution of Pulses of Normal Young Men under Various Conditions.*

index. Figure 5 shows no satisfactory relation between the sitting systolic blood pressure and the fitness index. Systolic blood pressures equal to or above 140 mm. are found in subjects who rank poor, average or good in fitness, and systolic blood pressures of 110 mm. or less are also found in the various groups.

Therefore, there is obviously no satisfactory relation between physical fitness for hard work and basal or sitting pulse rates or sitting blood pressures. In contrast, the pulse during recovery from hard exercise shows a good relation to a man's fitness for strenuous exertion.

Influence of Emotional Factors on Resting Pulse and Blood Pressure

Although the influence of common emotional factors on the heart rate at rest is well known,[4, 10, 11] it is too often underestimated. The two following

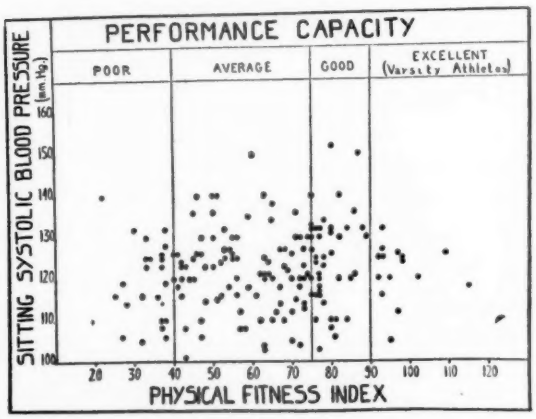

Figure 5. *Sitting Systolic Blood Pressure in Relation to Performance Capacity and Physical-Fitness Index. It should be noted no significant relation exists between these measurements.*

sets of results emphasize the importance of these factors in determining the heart rate of subjects who are not actually working.

The sitting pulse was recorded on 231 subjects resting for ten minutes before the treadmill run but after a warming up, which consisted in walking at 3 miles per hour, grade 8.6 per cent, on the treadmill. In 61 of them the lowest pulse was above 100 beats per minute. Fourteen of the latter men were poorly fit, 36 were average, 10 were good, and 1 was excellent. In comparison, the men who had pulse rates well below 100 under the same conditions had a similar performance capacity. Since no physical work accompanied the rise of pulse, it is seen that the emotional effect of being tested was the factor responsible for the increase of heart rate. The conclusion that this is an emotional effect* is further illustrated by the fact that 20 per cent of the subjects had a lower heart rate during the rest period after walking on the treadmill than before walking, and that about 10 per cent of them had a lower sitting pulse five to seven minutes after an exhausting run than before the run. Such findings clearly indicate that in these subjects the high heart rates before the test were due to persistent emotional stimulation.

Heart rates were also recorded by the cardiotachometer before the beginning of the treadmill run, with the subject standing on the treadmill ready to go but motionless. The pulse per minute was derived from twelve-second recordings. Under these conditions the average pulse in 170 students was 125, with a range from 82 to 165 (Fig. 4). Only 8 subjects had a pulse below 100. Four minutes after the treadmill run the average pulse was only 113 with a range from 78 to 150.

The same phenomenon can be observed both in nonathletic students and in well-trained athletes. For example, in the oarsmen the average pulse standing on the treadmill was 120 (extremes 108 to 135), and four minutes after the run it was reduced to 96 (extremes 63 to 108). In 30 cross-country runners, the average pulse standing on the treadmill was 114 (extremes 96 to 140), and four minutes after the run it was 101 (extremes 80 to 120) (Table 1).

These observations show that in young men emotional factors markedly influence the heart rate at rest before a test of physical fitness. Such factors are probably largely responsible in determining the heart rate during the course of a routine medical examination.

Similar observations have been made by Dr. J. R. Gallagher,[12] of Phillips Academy, Andover, Massachusetts, on boys ranging from twelve to eighteen years of age. The resting pulse taken at the time of the annual medical examination varied from 48 to 125. Eighteen boys out of 726 had pulse rates persistently over 100. In 14 of them the pulse was between 100 and 109, 2 had pulse rates between 110 and 119, and 2 had resting pulse rates between 120 and 125. Furthermore, 11 boys had resting systolic blood pressures of 140 mm. or more. The increase of pulse before the test of physical fitness was regularly observed. All of them nevertheless were medically normal and well within the usual range of physical fitness for that age group, as measured by their actual capacity to perform a standard amount of hard work.

Summary and Conclusions

There is a wide variation in pulse and blood pressure in normal, healthy young men. Although the values far exceed the usually accepted norms, they are nevertheless compatible with nor-

*The term "emotional effect," as employed here, in no way conveys the meaning of psychoneurosis or other psychiatric abnormality. It refers to ordinary anticipatory apprehension and excitement and the variation in cardiovascular response that may accompany it. A detailed psychiatric study of these students, carried out for another purpose, revealed no essential emotional instability.

mal physiologic reactions to emotional stress and hard muscular work.

There is no satisfactory relation between basal pulse, sitting pulse and physical fitness for strenuous exertion in normal, healthy young men.

There is no relation between sitting systolic or diastolic blood pressure and physical fitness for strenuous exertion in normal, healthy young men.

Emotional factors are largely responsible for high resting pulse rates commonly found during the preinduction medical examination of healthy young men.

Resting pulses above 100 and sitting systolic blood pressures above 140 mm. are not exceptional in medically normal subjects when exposed to some emotional strain and in many of them they accompany an average or good physical fitness for hard muscular work.

In normal young men no measurement of pulse or blood pressure, taken at rest, is indicative of capacity to perform hard work.

When the resting pulse or blood pressure is unusually high it is recommended that the subject be submitted to a standard amount of strenuous exercise. The estimate of capacity to do hard muscular work should be based on the subject's actual ability to perform it and on the speed of recovery of his heart after exercise, rather than on resting values of pulse and blood pressure alone.

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References

1. Cotton, F. S. Relation of athletic status to pulse rate in men and women. *J. Physiol.* 76:39-51, 1932.
2. White, P. D. Bradycardia (below rate of 40) in athletes, especially in long distance runners. *J. A. M. A.* 120:642, 1942.
3. Bock, A. V., VanCaulaert, C., Dill, D. B., Fölling, A., and Hurxthal, L. M. Studies in muscular activity: dynamical changes occurring in man at work. *J. Physiol.* 66:136-161, 1928.
4. Dill, D. B., and Brouha, L. Etude sur le rythme cardiaque pendant l'exercice. *Travail Humain* 5:3-19, 1937.
5. Robinson, S., Edwards, H. T., and Dill, D. B. New records in human power. *Science* 85:409, 1937.
6. Edwards, H. T., Brouha, L., and Johnson, R. E. Effets de l'entrainement sur le taux de l'acide lactique au cours du travail musculaire. *Travail Humain* 8:1-9, 1940.
7. Johnson, R. E., Brouha, L., and Darling, R. C. Test of physical fitness for strenuous exertion. *Rev. Can. Biol.* 1:491-503, 1942.
8. Metheny, E., Brouha, L., Johnson, R. E., and Forbes, W. H. Some physiologic responses of women and men to moderate and strenuous exercise. *Am. J. Physiol.* 137:318-326, 1942.
9. Brouha, L., Graybiel, A., and Heath, C. W. The step test: a simple method of measuring fitness for hard muscular work in adult man. *Rev. Can. Biol.* 2:86-91, 1943.
10. Krogh, A., and Lindhard, J. Regulation of respiration and circulation during initial stages of muscular work. *J. Physiol.* 47:112-136, 1913.
11. Merklen, L. *Le rythme du coeur au cours de l'activité musculaire.* 388 pp. Nancy: Camille Andre, 1926.
12. Gallagher, J. R. Personal communication.

DIABETES MELLITUS IN GENERAL PRACTICE*

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IN THE time allotted for this discussion I shall not dwell upon the history of diabetes mellitus, the older conceptions of the disease, or its displaced methods of diagnosis and treatment. It suffices to say that the knowledge of diabetes has come a long way from the time when it was the custom of physicians to decide that sugar was present in the urine from its syrupy appearance and sweet taste. It is doubtful if there is anyone present who has ever had the temerity to maintain that such a diagnosis could be made on that evidence alone. Yet the doctors of other days were not inhibited by refined sensibilities which we apparently possess to a greater degree, and no doubt we have sacrificed something of value in the process of evolution. I am assuming that every modern practitioner is aware of the method of diagnosis of diabetes long before the patient has reached the stage where there is inordinate thirst, excessive polyuria and marked loss of weight; and that all are aware of the value of routine urine examinations, of the taking of night and morning specimens in suspicious cases rather than a single specimen at any one time of day, and of blood chemistry both in diagnosis and during treatment. Within the experience of most of us has occurred the discovery of insulin and the revolutionizing of the treatment of diabetes, so that now it is rare for a patient to die from the effects of diabetes alone. To younger practitioners this is simply a matter of historical interest, since during their training and recent years of practice they have known no other way of approaching diabetes.

That so large a number of diabetic patients who previously would have died in the course of a few years now come within the age groups susceptible to cancer, arteriosclerosis, heart disease and other degenerative ailments affecting the vital statistics of these groups, is mentioned only in passing. Assuming, therefore, a general acquaintance with the essential knowledge of diabetes at present, — that is, its symptoms, its effects and the tests required to confirm its presence, I approach the subject with the flat assertion that *any general practitioner* who will give the time and thought to diabetes that it requires is qualified to treat the disease on relatively equal terms with the specialist. The average case that goes along smoothly with the diabetic expert

*Read at a meeting of the Worcester District Medical Society, Worcester, Massachusetts, April 15, 1942.

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should go just as smoothly with the general practitioner, and any case that baffles the latter likewise, and to the same extent, baffles the former.

In the majority of cases of diabetes, it is not essential to begin treatment with a period of hospitalization, although in many cases this is desirable. Only 9 patients of the series reported below have ever been hospitalized for any condition connected with diabetes. This policy will appear debatable to many, but these cases are presented exactly as they occurred.

Of the 63 cases covered by this paper, — 5 patients under five years of age are included, — only one is reported in each of several groups, formed according to type and severity. Except for minor variations, these cases are representative of the various groups.

Case 1. M. R. Y., a 47-year-old, unmarried woman, was first seen on August 15, 1938. She had lost 25 pounds in the previous 4 months. She tired easily during the previous 2 months, but had no headache or sleepiness, and had moderate thirst. She was nervous and irritable, slept badly, and had a poor appetite, and her bowels were normal. There was occasional nocturia. Five years previously she fell from a horse, receiving a possible fracture of the skull. She returned to her work as a nurse 1 month later, but had not been well since. The sense of smell was absent for 2 years and was still abnormal.

Physical examination showed a thin, poorly nourished woman 5 feet 5 inches in height and weighing 98 pounds. The pulse was 104 and the blood pressure 156/74. The urine showed a specific gravity of 1.040, was acid and contained no albumin and 5 per cent sugar. The fasting blood sugar was 212 mg. per 100 cc.

The patient was placed on a 1775-calorie diet and given insulin, 15 units three times a day. Four days later the blood sugar was 104 mg. per 100 cc. and the urine was negative for sugar. She was intelligent and co-operative, and understood perfectly the value of the diet for maintaining normal weight, and the necessity of daily watchfulness with regard to the urine. With the advent of protamine-zinc insulin the patient began taking it in daily doses of 30 units each, supplemented by 8 to 15 units of regular insulin when sugar showed in the urine at the noon or evening meal.

Subsequent blood-sugar readings ranged from 105 to 182 mg. These were first taken at monthly intervals, but are now taken only when there is a stubborn increase in the urinary sugar output. The weight has been maintained at 123 pounds, from which there is practically no variation. A high level of blood sugar has occurred only during the course of upper-respiratory irritation, or following trips away from home, during which the diet may be variable.

Case 2. F. B., a 64-year-old, married woman, was first seen on May 6, 1940, complaining of headache, exhaustion and pain in the legs. She had known for 11 years that her urine contained sugar, and during the last 2 years had been a patient in the Webber Hospital, Biddeford, Maine, and in the Deaconess Hospital, Boston. Control of her disease had apparently been difficult in both places, and she had been subject to almost daily insulin-shock reactions.

Physical examination showed a poorly nourished woman 5 feet 4 inches tall and weighing 94 pounds. The pulse was 88 and the blood pressure 194/110. There was marked arteriosclerosis.

It was decided that the patient would maintain her weight at 110 pounds on a 1775-calorie diet. The blood sugar at the beginning of treatment was 188 mg. per 100 cc. and the sugar in the urine 3 per cent. She was placed on a morning dose of 30 units of protamine-zinc insulin and 15 units of regular insulin. Although she insisted she could not eat the amount of food on her diet list, she was compelled to eat it. The weight rapidly rose to 109 pounds, and has been maintained at that point to the present time. One and a half grains of Digitora was given daily for irregularity of the heart, but nothing was done for the arteriosclerosis or hypertension. The urine was tested at noon and night, and an additional 15 to 18 units of regular insulin was given when sugar was present. Blood-sugar tests taken at intervals of two to four weeks showed variations from 100 to 232 mg. per 100 cc., the last high reading being on September 27, 1941.

The patient has had only two insulin reactions of a minor type, which followed the discovery of a blood sugar of 212 mg. in September, 1941, when the protamine-zinc insulin dose was increased to 40 units and the blood sugar dropped rapidly to 108 mg. Orange juice was effective in quickly combating these insulin shocks, and the blood sugar on October 18 being 100, the 30-unit dose was resumed. The patient at present shows a small trace of albumin in the urine, traces of sugar several times a week and a blood sugar of 130 mg. She is in excellent condition.

Case 3. M. H., a 67-year-old, married woman, was first seen on January 15, 1934, with a history of intermittent glycosuria since 1926. She complained of severe abdominal and epigastric pain, backache, headache and dizziness, with some sleepiness and weakness. Analgesics gave no relief for the pain, and urine examination showed large amounts of sugar. The blood-sugar content was 325 mg. per 100 cc.

On diet and insulin the body weight was reduced from 178 to 149 pounds, but as soon as the patient felt better, she refused to follow the prescribed diet or to take insulin in proper doses. At intervals of 4 to 6 months she had recurrences of abdominal pain. As a result she became more co-operative until once more free from symptoms, when she again broke all the rules. In 1941 she was hospitalized for gangrene of a toe, which was amputated. She is now sugar-free, but will undoubtedly break the rules again and have further trouble with her extremities.

Case 4. O. T., a 40-year-old, married woman, was first seen in 1922, when, at the age of 18, she had an acute attack of weakness, thirst, weight loss and large amounts of sugar in the urine. As often occurs in younger people developing diabetes, she requires at present in order to maintain her proper working weight relatively large doses of insulin, namely, 35 units of protamine-zinc insulin and 20 units of regular insulin before breakfast and 15 to 25 units of regular insulin before supper, according to the color test of the urine. However, she is able to do clerical work during the day, and in addition does her home cooking and housework. The blood sugar has ranged from 238 mg. to a maintenance level of 106 mg. per 100 cc.

Case 5. F. E. P., a 54-year-old man, first seen in 1932, developed symptoms of frequency of urination and pruritus on the inside of the thighs, with nocturia and a feeling of fatigue and thirst. The urine sugar was 5 per cent

and the blood sugar 294 mg. per 100 cc. With insulin and diet the blood-sugar level in 19 days was reduced to 150 mg., and for the following 3 months remained at about that level. Meanwhile the urine was sugar free. At a blood-sugar level of 111 mg., with sugar-free urine, insulin was discontinued and the urine remained sugar free for more than a year without the ingestion of more insulin. Since then, it has been necessary to give insulin for only 6 weeks out of each year.

Comment. This case exemplifies the oft-repeated observation that there is no definite relation between blood-sugar findings and urinary sugar: with a high urine sugar the blood sugar is often comparatively low, and *vice versa.*

Discussion

Among the 63 cases of diabetes treated in this series, there were 5 deaths (8 per cent). The average age at diagnosis was fifty-one years, and the average known duration of the disease was seven years. The latter figure is not a reliable index of actual duration, because no doubt many of the milder cases had existed for some time before discovery. The average age at present is fifty-eight, the youngest patient being twenty-four and the oldest seventy-eight. There were 7 men and 56 women. In 2 cases both husband and wife had diabetes. The average body weight at onset was 169 pounds, with the highest 235 and the lowest 90 pounds. The average weight at present is 150 pounds with the highest 190 and the lowest 110 pounds. The average daily intake of insulin is 22 units, with the highest 65 units. No insulin is now being taken in 6 cases, and less than 15 units in 2. The average blood sugar on diagnosis was 196 mg. per cent — the highest 325 mg. and the lowest 120 mg. The average maintained level of blood sugar in all cases was 120 mg., with the lowest 100 mg. and the highest 137 mg.

The causes of death were as follows: carcinoma of the liver and pancreas (age fifty-seven); general carcinomatosis with cerebral hemorrhage and paralysis (age sixty-nine); general carcinoma, myocardial failure with ascites (age sixty-eight); lobar pneumonia (age sixty-four); and coronary thrombosis (age sixty-seven).

Other diseases or conditions associated with diabetes at the time of diagnosis were: arteriosclerosis, 8 cases; cholelithiasis, 1 case (operated on and cured); cholecystitis, 1 case (not operated on); hypertensive heart disease, with or without valve lesions, 4 cases; vari ose veins, 5 cases; varicose ulcers, 1 case; arthritis, 5 cases; carcinoma, 3 cases (all the patients died of carcinoma within an eight-year period); hemorrhoids, 1 case; gangrene of great toe, 3 cases (one of these patients was operated on and the toe removed; another was removed to Florida and arrangements were made for her hospitalization; the third patient, whose diabetes was discovered at the time the gangrenous toe was observed, has, under the intensive use of insulin and care, preserved the toe, although it is expected that the slightest bruise or disturbance of the circulation will lead to its loss); myalgia, 1 case; pilonidal cyst, 1 case (operated on and cured); carbuncle of the neck, 1 case severe but cured); carbuncle of the shoulder, 1 case (very large, and in sloughing out left a large cavity, which was slow to heal).

With the control of diabetes there has been a marked decrease in diabetic mortality and an increase in the complicating diseases associated with it, particularly the carcinomas and degenerative diseases incident to the prolongation of life in these patients.

It may be said that diabetic patients who are treated well may carry on effectively and do work that is not noticeably less efficient than that of their diabetic-free neighbors. In fact, work is in itself excellent medicine. The nonintelligent diabetic patient presents a problem that can be solved only by having an intelligent member of the family watch the diet and supervise the testing of urine and the giving of insulin.

The classic definition of diabetes mellitus is "a metabolic disorder in which the ability to oxidize carbohydrates is more or less completely lost due to faulty pancreatic activity, especially of the islets of Langerhans." This produces hyperglycemia with resulting glycosuria and polyuria giving symptoms of thirst, hunger, emaciation and weakness and also imperfect combustion of fats with resulting acidosis, resulting in the symptoms of dyspnea, lipemia, ketonuria and finally coma. There may also be pruritus and lowered resistance to pyogenic infections. But the alert practitioner will diagnose many cases of diabetes mellitus long before these later symptoms appear. In fact, most cases should be diagnosed before the patient is markedly ill, or aware that he is sick. Routine urine examinations on all cases, either at home or in the doctor's office, should be done not later than the second call. In this way an unbelievable number of unsuspected cases of diabetes can be discovered.

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CLINICAL NOTE

ADDISON'S DISEASE: REPORT OF A FATAL CASE*

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THE following case report of fatal Addison's disease is presented because of the relative rarity of some of the findings, and because its occurrence in a soldier on active duty seems worthy of note.

CASE REPORT

C. P. N., a 29-year-old private in a military police company, was admitted to the Medical Service of the 48th Evacuation Hospital on September 11, 1942, for symptoms of shock of 12 hours' duration. The hospital was located near Murfreesboro, Tennessee, and was acting as an evacuation hospital for the training maneuvers of the Second Army.

The patient had been well until 4 days before admission, when he complained of nausea and vomiting. He was taken to a medical field station the night before admission, and a history of low-abdominal pain and constipation for a few days preceding was elicited. An enema was administered, and immediately after this the patient went into a state of shock. He was given shock treatment and appeared to improve considerably, but relapsed on the following morning and was evacuated to the hospital.

Subsequent to the death and autopsy, additional information was obtained from the patient's commanding officer to the effect that about 4 weeks before the terminal illness he complained of weakness, extreme fatigability, abdominal pain, diarrhea and nervous irritability, and became exceptionally pale. He was sent to sick call on August 14 and again on September 3, at which time marked fatigability and weakness were noted. On the latter day he went on a short hike with his company, but had to be returned to the company area because of weakness.

On physical examination at admission the patient appeared extremely weak, but was able to talk rationally. The temperature was 97.5°F., the pulse 140 and feeble. The systolic blood pressure was 80. The head showed no signs of external violence. The pupils reacted to light and were of normal size. Both eyeballs were soft and sunken into the orbits. The ears, nose and throat were normal. No mucosal pigmentation was noted. The breath had an acetone odor. The skin was pale, cool and dusky. The mucous membranes and nailbeds were cyanotic. No abnormal cutaneous pigmentation was noted. The neck showed no stiffness or enlarged nodes. The heart was normal in size. The sounds were faint and no murmurs were heard. The lungs were resonant. Breath sounds were heard with difficulty because of shallow respirations. There were no rales. The abdomen was negative. The extremities showed no edema. The tendon reflexes were absent. There were no abnormal reflexes.

The white-cell count was 14,700, with 56 per cent (2 per cent segmented and 54 per cent stab forms) neutrophilic leukocytes, 40 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils.

The admission diagnosis was shock and dehydration of undetermined origin. Among the possible causes suggested were overwhelming sepsis, poisoning, rupture of the colon or other viscus and acute adrenal insufficiency.

The patient received 2000 cc. of 5 per cent glucose in normal saline solution intravenously, two ampules of caffein sodium benzoate intramuscularly, warmth, and elevation of the lower extremities. Nasal oxygen was administered, which relieved the cyanosis. Soon after admission the pulse became imperceptible and the blood pressure unobtainable. Over the course of the next few hours the patient's condition grew rapidly worse. No urine could be obtained, even with an indwelling catheter. The respirations became rapid, and moist rales were audible in the lungs. The skin remained cool. The patient's mental state became clouded, coma supervened, and he died 6 hours after admission. A blood culture taken post mortem was negative; the nonprotein nitrogen was 36 mg., the blood sugar 109 mg., and the urea nitrogen 11 mg. per 100 cc.†

Autopsy (performed 3 hours after death). The following is a summary of the gross findings, which were as follows:

The body appeared well developed and well nourished, but the infrahollows appeared increased. The hair was prematurely gray. The subcutaneous fat appeared to be of normal thickness. Abnormal pigmentation of the skin and mucous membranes was not found. The parietal and visceral pleura were adherent owing to diffuse fibrous adhesions on all surfaces, which were separated by blunt dissection with great difficulty. The interlobar pleural surfaces showed similar adhesions.

The right lung weighed 704 gm. and the left lung 640 gm. Both lungs showed markedly thickened pleura, especially over the upper lobes. A few pea-sized, blackish perihilar nodes were noted that showed no caseation or calcification on section. All the bronchi were filled with bloody froth. The parenchyma was hyperemic, especially in the lower lobes. There was no evidence of chronic parenchymatous disease.

The heart weighed 320 gm. and showed no abnormalities. The aorta was normal. The periaortic nodes of the thoracic aorta were increased in size and number. No caseation was seen on section. The spleen weighed 210 gm. and showed no abnormalities. The liver weighed 1664 gm. There were no abnormalities in the liver, pancreas, gastrointestinal tract or kidneys, each of which weighed 160 gm. The lymph nodes of the mesenteric root appeared slightly increased in size and number. They showed no caseation on section.

The adrenal glands both showed identical findings and were surrounded by indurated fat. The capsules were markedly thickened. The parenchyma was almost entirely replaced by grayish, cheesy, crumbly material, which showed a tendency to shell out. No remaining medulla was discernible, but in one area in the right gland there was a small island of apparently normal cortex. Crushings of the cheeselike material from each gland were negative for acid-fast bacilli.

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†These examinations were performed by H. T. Hart, United States Veterans' Hospital, Murfreesboro, Tennessee.

Gross diagnoses: Bilateral caseous tuberculosis of adrenal glands; acute pulmonary hyperemia; bilateral chronic fibrous pleuritis.

Microscopic examination was performed by the laboratory of the Lawson General Hospital, Atlanta, Georgia. It was reported as follows:

> The adrenal glands are almost entirely destroyed. They have been replaced with a necrotic granulomatous tissue appearing fairly characteristic of tuberculosis. Ziehl–Neelsen stain revealed a rare tubercle bacillus. A hilus lymph node and one other node show a chronic tuberculosis. Other nodes are not involved. The sections of lungs show acute congestion with no evidence of tuberculosis. The sections of the heart, liver, kidney and spleen appear essentially normal.
>
> Anatomical diagnoses: Tuberculosis of adrenal glands (Addison's disease); tuberculous lymphadenitis.

The Army Medical Museum in a communication to the Lawson General Hospital reviewed this case as follows:

> Diagnosis: Addison's disease secondary to bilateral involvement of the adrenal glands. The latter present characteristic areas of caseation necrosis with typical tubercle formation. The greater portion of the cortex is completely destroyed in this process, although occasionally small hyperplastic accumulations of cortical cells still persist. In the lymph nodes one recognizes not only tuberculous foci but in addition small areas of amyloid deposition. It is interesting to note the absence of any recent tuberculous lesion in the lung.

Discussion

The absence of visible abnormal pigmentation in this patient is contrary to the usual expectation. Although Lewin (quoted by Grollman[1]) found pigmentation in only 72 per cent of his autopsied cases, this figure is generally held to be far too low. Thus Rowntree and Snell[2] in their series of 108 cases had only 1 case without pigmentation, and Means[3] states that only rarely are cases of the chronic form found without pigmentation. Pigmentation is generally one of the first symptoms to appear and may, in fact, antedate other symptoms by months or even years. In this case, although symptomatically of short duration, the destructive process in the adrenal glands was undoubtedly chronic, and should have afforded ample time for the formation of the abnormal pigmentation. The cause of the pathologic pigmentation in Addison's disease has never been satisfactorily explained,[4] and hence no theory can be advanced for its nonappearance in this case.

Another aspect of this case worthy of note is the relatively short duration of the clinical symptoms. The case of shortest duration on record is eighteen days.[5] Our patient made his first appearance at sick call four weeks before admission, and was not sick enough to warrant hospitalization until the night before his death. This is especially significant, because it is usual Army procedure, especially when troops are on maneuvers, to evacuate and hospitalize personnel not capable of full duty. There was no known precipitating factor such as infection, exposure or medication to account for the sudden fatal Addisonian crisis. It seems unlikely that such trivial bodily trauma as that caused by an enema could have been the precipitating factor.

It is remarkable that the patient continued active as long as he did, in view of the practically complete destruction of adrenal tissue. As no adrenal rests were detected at autopsy, it can be inferred that the minute hyperplastic remnants of cortex produced sufficient hormone to maintain life and a fair degree of activity.

No facilities for the analysis of the blood sodium or chloride were available, but it is noteworthy that the results of the blood chemical tests that were made were contrary to the usual findings in Addisonian crisis. There was no abnormal nitrogen retention or hypoglycemia.

A similar case is cited by Boyd.[4] This patient was also a soldier and was carrying on his duties in a camp. He was found in a semiconscious state and died in a few hours. The adrenal glands were found to have been completely destroyed by tuberculosis, and there was no trace of pigmentation.

Summary

A case of rapidly fatal Addisonian crisis due to tuberculosis of the adrenal glands in a soldier on active duty is reported as noteworthy, because of the complete absence of pathologic pigmentation, normal blood sugar and blood urea nitrogen and an ascertainable clinical history of only four weeks.

References

1. Grollman, A. *The Adrenals.* 122 pp. Baltimore: Williams & Wilkins Company, 1936.
2. Rowntree, L. G., and Snell, A. *A Clinical Study of Addison's Disease.* 317 pp. Philadelphia: W. B. Saunders Company, 1931.
3. Means, J. H. Addison's disease. Musser's *Internal Medicine.* Third edition. 1428 pp. Philadelphia: Lea & Febiger, 1938. Pp. 903-907.
4. Boyd, W. *Pathology of Internal Diseases.* Third edition. 874 pp. Philadelphia: Lea & Febiger, 1940.
5. Rowntree, L. G. Addison's disease. Cecil's *Textbook of Medicine.* Fifth edition. 1744 pp. Philadelphia: W. B. Saunders Company, 1940. Pp. 1330-1338.

MEDICAL PROGRESS

ISOTOPES IN MEDICAL INVESTIGATION AND THERAPY (Concluded)*

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EYE

THE prevention and treatment of glaucoma and of many other ophthalmologic diseases can be placed on a sound physiologic basis only when there is a complete understanding of the mechanisms of water and ionic exchange between the fluids of the eye and the blood stream. Important contributions to the current knowledge of such exchange have been made by Kinsey, Grant and Cogan.[23] These investigators injected heavy water intravenously into rabbits and followed its appearance in the aqueous and vitreous of the eye. In another series of experiments, they replaced some of the fluid of the aqueous and vitreous with isotonic sodium chloride containing heavy water and traced the disappearance of the labeled material from the eye. Exchange of water between the aqueous and the blood was extremely rapid, half of the water content of this fluid being replaced in less than three minutes, a rate of exchange fifty times greater than that previously reported for the rate of formation for the whole aqueous.

The quantity of water going from the aqueous to the vitreous and to the lens was found to represent only a small portion of the total water movement out of the aqueous. The rate of exchange of water by the vitreous was considerably slower, ten to fifteen minutes being required for a 50 per cent replacement.

Net transfer of water through the cornea has been believed to occur only from the posterior to the anterior surface, the direction of transfer apparently being determined by the integrity of the corneal epithelium, which maintains osmotic pressure by its semipermeability. Previous attempts to demonstrate passage of water in the anteroposterior direction have been unsuccessful because bullae and epithelial damage resulted as soon as the concentration of sodium chloride became greater on the posterior surface of the cornea than it was on the anterior surface. Using heavy water, it has been shown that water passes through the cornea in both directions, but that the normal epithelium is essentially impermeable to passage of sodium chloride in either direction.[24]

Radioactive sodium, chloride and phosphorus passed into the anterior chamber much more slowly than did water.[25] The sodium and chloride ions entered the anterior chamber at a rate calculated to be equivalent to 4 cu. mm. per minute of whole aqueous, a rate that is of the same order of magnitude as the rate of formation of the whole aqueous. These findings indicate that "the apparent rates of aqueous formation are more directly concerned with electrolyte net volume changes than with water movement, which is only coincidental."

TEETH

Interest in the pathologic physiology of dental caries has stimulated considerable investigation of the mineral metabolism of the teeth. To date much of this work has been concerned with determining the mode of deposition of phosphate in the enamel and dentin. Early in vitro studies showed that both the dentin and enamel adsorbed phosphates from aqueous solutions, the phosphate ions being deposited on a crystal latticework of hydroxyapatite in such fashion that the calcium-phosphate ratio was maintained at 2.10 in both tissues, although deposition occurred more rapidly and in larger amounts in the dentin than it did in the enamel.[26] These findings suggested that adsorption of various minerals from the saliva might occur, and animal experimentation demonstrated this fact. Sognnaes and Volker[27] found that radioactive phosphorus appearing in the surface layers of enamel in various animals was definitely adsorbed from the saliva. Larger amounts of phosphate were deposited in the dentin, and it was believed that it reached this tissue from the blood stream. More recent studies by Barnum and Armstrong[28] showed that although some of the phosphate of the enamel was adsorbed from the

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*. Volume III. 678 pp. Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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saliva, the major portion was derived from the blood and passed through the dentin before reaching the enamel. They also found, however, that phosphate could pass from the saliva through the enamel and into the dentin. These findings held for mature nongrowing teeth as well as for the actively growing teeth of young animals, proving that even the highly mineralized dental enamel is not static but is in a state of constant mineral exchange and replacement.

Fluorides are in some way related to the inhibition of dental caries. The addition of a fluoride to caries-producing diets greatly decreases the incidence of dental caries. Persons living in districts in which water and diet contain large quantities of fluorides develop dental caries much less frequently than do the inhabitants of areas in which fluoride concentration is normal or low; and finally, chemical analyses show that the enamel of sound teeth contains more fluoride than does carious enamel. These facts suggest that dental caries might be prevented or controlled if fluoride could be deposited therapeutically in the enamel. Volker and his associates[29] showed that significant amounts of fluoride were deposited in the enamel after parenteral administration or after local application of fluoride solutions directly to the teeth. The possible widespread prophylactic or therapeutic use of fluorides has at least one serious drawback, however, since deposition of even small amounts of fluoride in the teeth produces an extremely unsightly, although harmless, condition known as "mottled enamel" or "dental fluorosis."

Circulation of Blood and Splenic Function

The blood volumes of animals and of human subjects have been determined by injecting erythrocytes labeled with radioactive iron[30, 31] or radioactive phosphorus[32] into experimental subjects and determining dilution of radioactivity produced by the blood of the recipient. Such experiments indicated that the actual volume of erythrocytes present in the circulatory system was only three quarters of the volume calculated by the dye-dilution technic. This entire volume of cells appeared to be in active circulation, and there was no evidence that cells were stored in the spleen or in any other hypothesized reservoir.[30]

A constant relation between the volume of cells in the circulation and the venous hematocrit has been demonstrated by Hahn and Bale.[33] These investigators[34] also showed that the total blood volume of the dog was constant, in spite of the marked variations in the relative proportions of cells and plasma that occurred during periods of anemia.

The astonishing fact that in the guinea pig a volume of water equal to 66 per cent of the total blood volume was exchanged with the extravascular fluid every minute was demonstrated by Flexner, Gellhorn and Merrell.[35] The great rapidity of this exchange was discovered by injecting heavy water intravenously and determining the length of time required for establishment of equilibrium between the blood and the extravascular fluid. Similar technics could readily be applied to human subjects using not only heavy water but labeled electrolytes and other substances. Such experiments would be of interest in studying conditions in which there is a supposed disturbance of vascular permeability.

An objective method for determining the circulation time in infants and children has been developed by Hubbard, Preston and Ross.[36] Radioactive sodium was injected intravenously into the antecubital vein of one arm, and the length of time required for radioactivity to appear in the blood of the other arm was measured. Although this method appears feasible, technical complexities limit its extensive use, and it is probable that the much more easily performed fluorescin method is just as reliable.

It has been assumed that the spleen serves as a reservoir for the storage of a large volume of erythrocytes, and that by muscular contraction it can express these stored cells into the circulation during times of stress. The finding that all the erythrocytes in the vascular system appear to be in active circulation[30] casts doubt on this theory. Experiments with radioactively tagged erythrocytes demonstrated that adrenalin injection and exercise did not produce any increase in the total volume of circulating erythrocytes, even though these procedures caused transient increases in the hematocrit.[37, 38] Ross and Chapin[39] found that the increase in the hematocrit produced by injecting adrenalin intravenously into human subjects was associated with a simultaneous and identical increase in the concentration of the plasma proteins, and that these changes were not influenced by splenectomy. They suggested that this hematocrit change is the result of hemoconcentration and not of splenic contraction, and concluded that the spleen does not function as a reservoir for the storage of any significant volume of erythrocytes.

Erythrocytes

The rapidity with which hemoglobin can be formed was indicated by the appearance of radioactive iron in the hemoglobin of circulating erythrocytes four hours after the isotope had been ingested.[40, 41] Since the iron of the hemoglobin molecule does not exchange with plasma or tissue

iron,[42] this observation showed either that the mature red blood cell synthesized hemoglobin, or that the rate of maturation of the cell was extremely rapid. The administration of large quantities of iron therapeutically accelerated the rate at which labeled iron was incorporated in erythrocytes, suggesting a stimulating effect of iron on hematopoiesis.[40]

The iron liberated by the breakdown of erythrocytes is rapidly reutilized by newly formed erythrocytes in preference to iron present in the usual tissue stores.[43] Although the exact interpretation of this finding is not clear, it may indicate that the hematopoietic system is able to reutilize some of the iron-containing products of hemoglobin breakdown before they have been completely degraded.

Intermediary Metabolism

The entire concept of the intermediary metabolism of carbohydrate, protein and fat and of the intricate biochemical processes by which life itself is maintained must be completely revised. The theory of independent exogenous and endogenous types of metabolism, the first concerned with wear and tear and replacement of the structures of the body, and the second with the supply of energy by combustion of foodstuffs, must be abandoned. In its place one must substitute the concept of a dynamic body equilibrium, a delicately balanced and infinitely complex chemical system in which all reactions are interdependent, but so adjusted that the body components remain constant in total amount and structure.

This fundamental and revolutionary revision of the concepts of metabolism has been brought about chiefly by the epoch-making experiments of Schoenheimer and his associates, employing heavy isotopes as labeling agents. In a series of well-integrated experiments, these investigators demonstrated that all body constituents are in a state of constant flux and change. Schoenheimer[44] has concisely summarized these contributions in the following paragraph:

> The large and complex molecules and their component units, fatty acids, aminoacids and nucleic acids, are constantly involved in rapid chemical reactions. Ester, peptide and other linkages open; the fragments thereby liberated merge with those derived from other large molecules, and with those absorbed from the intestinal tract, to form a metabolic pool of components indistinguishable as to origin. These liberated molecules are again subject to numerous processes. Fatty acids are dehydrogenated, degraded or elongated, and thereby continually interconverted. While some individual molecules of these acids are completely degraded, other individuals of the same chemical species are steadily formed from entirely different substances, notably from carbohydrate. Similar reactions occur among the split products of the proteins. The free aminoacids are deaminated, and the nitrogen liberated is transferred to other previously deaminated molecules to form new aminoacids. Part of the pool of newly formed small molecules constantly re-enters vacant places in the large molecules to restore the fats, the proteins and the nucleoproteins. Some of the small molecules involved in these regeneration reactions constitute intermediate steps in the formation of excretory products.

The intermediary metabolic reactions of sulfur-containing compounds[45] and of phospholipids[46] also conformed to the concept of metabolic regeneration.

The ability of the animal organism to utilize the completely oxidized carbon atom of carbon dioxide for the synthesis of glycogen has been demonstrated by Hastings and his associates.[47, 48] They injected a solution of sodium bicarbonate labeled with radioactive carbon into rats and subsequently detected the labeled carbon atoms in glycogen isolated from the liver, a truly revolutionary discovery, since all previous concepts of carbohydrate metabolism had regarded the completely oxidized carbon of carbon dioxide as a waste product.

In subsequent experiments[49–51] it was discovered that carbon dioxide entered into the formation of glycogen by a process of condensation with pyruvic acid to provide the 4-carbon acids essential for glycogen synthesis. Other investigators[52] found that isolated slices of liver tissue retained the ability to convert carbon dioxide into carboxyl and carbonyl carbon. The architectural structure of the liver was not essential for this conversion, since it occurred in both minced liver tissue and cell-free liver extracts.[53]

The importance of these experiments can scarcely be overestimated, since they necessitate complete revision of our present concepts of carbohydrate metabolism.

Therapeutic Applications

Radioactive isotopes are effective therapeutic agents only if they are selectively deposited in the neoplastic or hyperplastic tissue that is to be destroyed. They must be deposited in such tissue in a much higher concentration than in normal tissue if radiation is to destroy the diseased tissue but not the normal tissue. Finally, the radiations that such isotopes emit must be strong enough to inhibit the growth of or actually to destroy the cells. To date only three isotopes, radioactive phosphorus, radioactive iodine and radioactive strontium, have fulfilled these requirements.

Radioactive phosphorus is deposited in high concentration in the rapidly growing cells of leu-

kemic and lymphomatous tumors as well as in the bone marrow and bone of leukemic and polycythemic patients.[54, 55] In these sites it liberates fairly destructive radiations that inhibit or destroy the actively growing tumor and bone-marrow cells. Radioactive phosphorus has been used extensively in the treatment of malignant diseases of the leukemia-lymphoma type by several groups of investigators,[56–59] who have recently summarized their experiences with 300 patients so treated. Their reports are fairly uniform concerning the effectiveness of the therapy in various diseases. Radioactive phosphorus is undoubtedly of considerable value in the treatment of lymphosarcoma and the chronic forms of myelogenous and lymphatic leukemia. It has on a few occasions produced remarkable remissions in acute leukemia but, on the whole, has been no more satisfactory than x-ray treatment in the control of the disease. Primary and metastatic carcinoma, Hodgkin's disease, multiple myeloma, reticulum-cell sarcoma and malignant melanoma have failed to show any appreciable response to treatment with radioactive phosphorus. Polycythemia vera frequently responds fairly well to large doses of the radioactive isotope, but judging from the case reports, the subjective improvement in these patients is considerably greater than is the hematologic response.

Sound criteria for the selection of patients who may be expected to benefit from radioactive phosphorus treatment have been formulated by investigators of the Memorial Hospital[59] and the Crocker Radiation Laboratory.[57] Proper selection of patients and careful regulation of dosage[57, 60] will, no doubt, increase the beneficial results of this form of treatment, although it is likely that radioactive phosphorus will continue to be only a palliative agent for a relatively few types of disease.

On theoretical grounds, hyperthyroidism should be readily amenable to treatment with radioactive iodine. Iodine is localized specifically in the thyroid gland, and to a greater degree in hyperplastic thyroid tissue than in normal thyroid tissue. Its radiations are fairly destructive, and in experimental animals complete necrosis of the entire thyroid gland has been produced with radioactive iodine.[61] Unlike the universally fatal disease, leukemia, hyperthyroidism is amenable to surgical treatment, and as a consequence clinical investigators have been extremely cautious in their use of radioactive iodine therapeutically, since overdosage may result in complete destruction of the gland and cause the subsequent development of myxedema. In several cases (as yet unreported in the literature), thyrotoxic patients have been given radioactive iodine with remarkable benefit. There is every reason to believe that in the not too distant future radioactive-iodine therapy may supplant subtotal thyroidectomy in the control of hyperthyroidism.

Radioactive strontium and radioactive calcium are metabolized in similar fashion by the animal organism,[62] and both are deposited in high concentration in the actively growing bone of osteoblastic metastatic carcinoma and osteogenic sarcoma.[63] The radiations of radioactive calcium are too weak to produce any therapeutic effect, but radioactive strontium emits powerful beta rays and should theoretically be of considerable value in the treatment of primary and secondary osteoblastic bone tumors. A preliminary report of the clinical use of radioactive strontium records its beneficial effect in a patient with metastatic carcinoma of the prostate.[63] Following intravenous injection of this substance there was cessation of pain, arrest of bone destruction and a marked drop in the serum-phosphatase level.

Six patients with osteogenic sarcoma were given injections of radioactive strontium.[63] The periods of observation were too short to permit adequate evaluation of the clinical effects of the therapy, but rapid and specific localization of the strontium in the actively growing tumor tissue did occur. Because of the marked radio-resistance of this type of tumor, it is doubtful whether any marked clinical benefit can be produced by this form of treatment, but it is quite probable that it will prove of some therapeutic value when used in conjunction with x-radiation.

* * *

Through the theoretically simple and technically not too difficult procedure of labeling foodstuffs, intermediary metabolic products, hormones and even tissues, it has become possible to follow the metabolic and functional interactions of these materials in normal organisms. Information so gained has completely revised many of our fundamental concepts of the biochemical and physiologic activities of living organisms. Application of this technic to the study of human disease has already provided the physician with new and effective therapeutic agents, and yet the possibilities of this technic have scarcely been realized by the majority of laboratory and clinical investigators. Extension of this method of investigation to new fields will undoubtedly yield even more fundamental and more widely practical information than has already been obtained.

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References

23. Kinsey, V. E., Grant, M., and Cogan, D. G. Water movement and the eye. *Arch. Ophth.* 27:242-252, 1942.
24. Cogan, D. G., and Kinsey, V. E. Cornea: transfer of water and sodium chloride by osmosis and diffusion through excised cornea. *Arch. Ophth.* 27:466-476, 1942.
25. Kinsey, V. E., Grant, M., Cogan, D. G., Livingood, J. J., and Curtis, B. R. Sodium chloride and phosphorus movement and the eye determined by radioactive isotopes. *Arch. Ophth.* 27:1126-1131, 1942.
26. Hodge, H. C., Van Huysen, R., Bonner, J. F., and Van Voorhis, S. N. Adsorption of phosphates at forty degrees by enamel, dentin, bone, and hydroxyapatite as shown by radioactive isotope. *J. Biol. Chem.* 138:451-457, 1941.
27. Sognnaes, R. F., and Volker, J. F. Studies on redistribution of radioactive phosphorus in tooth enamel of experimental animals. *Am. J. Physiol.* 133:112-120, 1941.
28. Barnum, C. P., and Armstrong, W. D. In vivo and in vitro exchange of phosphorus by enamel and dentin. *Am. J. Physiol.* 135:478-484, 1942.
29. Volker, J. F., Hodge, H. C., Wilson, H. J., and Van Voorhis, S. N. Adsorption of fluorides by enamel, dentin, bone, and hydroxyapatite as shown by radioactive isotope. *J. Biol. Chem.* 134:543-548, 1940.
30. Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M., and Whipple, G. H. Red cell and plasma volumes (circulating and total) as determined by radio iron and by dye. *J. Exper. Med.* 75:221-232, 1942.
31. Ross, J. F., and Chapin, M. A. Direct determination of erythrocyte volume in human subjects with radioactively tagged cells. *Fed. Proc.* 1:183, 1942.
32. Anderson, R. S. Use of radioactive phosphorus for determining total circulating erythrocyte volumes. *Am. J. Physiol.* 137:539-543, 1942.
33. Hahn, P. F., and Bale, W. F. Linear relationship between circulating red cell mass and venous hematocrit as determined with radioactive iron. *Am. J. Physiol.* 136:314-317, 1942.
34. Hahn, P. F., Bale, W. F., and Balfour, W. M. Radioactive iron used to study red blood cells over long periods; the constancy of the total blood volume in dog. *Am. J. Physiol.* 135:600-605, 1942.
35. Flexner, L. B., Gellhorn, A., and Merrell, M. Studies on rates of exchange of substances between blood and extravascular fluid: exchange of water in guinea pig. *J. Biol. Chem.* 144:35-40, 1942.
36. Hubbard, J. P., Preston, W. N., and Ross, R. A. Velocity of blood flow in infants and young children determined by radioactive sodium. *J. Clin. Investigation* 21:613-617, 1942.
37. Ross, J. F., and Chapin, M. A. Absence of erythrocyte reserves in human subjects as indicated with radioactive tagged cells. *J. Clin. Investigation* 21:640, 1942.
38. Hahn, P. F., Bale, W. F., and Bonner, J. F., Jr. Mechanism of effect of epinephrine on venous hematocrit value of normal unanesthetised dog. *Am. J. Physiol.* 137:717-721, 1942.
39. Ross, J. F., and Chapin, M. A. Unpublished data.
40. Hahn, P. F., Ross, J. F., Bale, W. F., and Whipple, G. H. Utilization of iron and rapidity of hemoglobin formation in anemia due to blood loss. *J. Exper. Med.* 71:731-736, 1940.
41. Miller, L. L., and Hahn, P. F. Appearance of radioactive iron as hemoglobin in red cell: significance of "easily split" iron. *J. Biol. Chem.* 134:585-590, 1940.
42. Hahn, P. F., Bale, W. F., Ross, J. F., Hettig, R. D., and Whipple, G. H. Radio-iron in plasma does not exchange with hemoglobin iron in red cells. *Science* 92:131, 1940.
43. Cruz, W. O., Hahn, P. F., and Bale, W. F. Hemoglobin radioactive iron liberated by erythrocyte destruction (acetylphenylhydrazine) promptly reutilized to form new hemoglobin. *Am. J. Physiol.* 135:595-599, 1942.
44. Schoenheimer, R. *Dynamic State of Body Constituents.* 78 pp. Cambridge: Harvard University Press. P. 62.
45. Tarver, H., and Schmidt, C. L. A. Radioactive sulfur studies: synthesis of methionine; conversion of methionine sulfur to taurine sulfur in dogs and rats; distribution of sulfur in proteins of animals fed sulfur or methionine; experiments in vitro with sulfur and hydrogen sulfide. *J. Biol. Chem.* 146:69-84, 1942.
46. Chaikoff, I. L. Application of labelling agents to the study of phospholipid metabolism. *Physiol. Rev.* 22:291-317, 1942.
47. Conant, J. B., Cramer, R. D., Hastings, A. B., Klemperer, F. W., Solomon, A. K., and Vennesland, B. Metabolism of lactic acid containing radioactive carboxyl carbon. *J. Biol. Chem.* 137:557-566, 1941.
48. Solomon, A. K., Vennesland, B., Klemperer, F. W., Buchanan, J. M., and Hastings, A. B. Participation of carbon dioxide in carbohydrate cycle. *J. Biol. Chem.* 140:171-182, 1941.
49. Vennesland, B., Solomon, A. K., Buchanan, J. M., Cramer, R. D., and Hastings, A. B. Metabolism of lactic acid containing radioactive carbon in the α or β position. *J. Biol. Chem.* 142:371-377, 1942.
50. Vennesland, B., Solomon, A. K., Buchanan, J. M., and Hastings, A. B. Glycogen formation from glucose in presence of radioactive carbon dioxide. *J. Biol. Chem.* 142:379-386, 1942.
51. Buchanan, J. M., Hastings, A. B., and Nesbett, F. B. Glycogen formation from pyruvate in vitro in presence of radioactive carbon dioxide. *J. Biol. Chem.* 145:715, 1942.
52. Evans, E. A., and Slotin, L. Carbon dioxide utilization by pigeon liver. *J. Biol. Chem.* 141:439-450, 1941.
53. Evans, E. A., Slotin, L., and Vennesland, B. Carbon dioxide assimilation in cell-free liver extracts. *J. Biol. Chem.* 143:565, 1942.
54. Erf, L. A., and Tuttle, L. W. Phosphorus metabolism of blood of patients with leukemia and polycythemia. *Am. J. M. Sc.* 203:83-87, 1942.
55. Erf, L. A. Clinical studies with aid of radiophosphorus: retention of radiophosphorus by tissues of patients dead of leukemia. *Am. J. M. Sc.* 203:529-535, 1942.
56. Craver, L. F. Treatment of leukemia by radioactive phosphorus. *Bull. N. Y. Acad. Med.* 18:254-262, 1942.
57. Low-Beer, B. V. A., Lawrence, J. H., and Stone, R. S. Therapeutic use of artificially produced radioactive substances: radiophosphorus, radiostrontium, radioiodine, with special reference to leukemia and allied diseases. *Radiology* 39:573-597, 1942.
58. Fitz-Hugh, T., Jr., and Hodes, P. J. Clinical experience with radiophosphorus in treatment of certain blood dyscrasias. *Am. J. M. Sc.* 204:662-665, 1942.
59. Kenney, J. M., and Craver, L. F. Further experiences in treatment of lymphosarcoma with radioactive phosphorus. *Radiology* 39:598-607, 1942.
60. Marinelli, L. D. Dosage determinations with radioactive isotopes. *Am. J. Roentgenol.* 47:210-216, 1942.
61. Hamilton, J. G. Use of radioactive tracers in biology and medicine. *Radiology* 39:541-572, 1942.
62. Pecher, C. Biological investigations with radioactive calcium and strontium. *Proc. Soc. Exper. Biol. & Med.* 49:86-91, 1941.
63. Treadwell, A. de G., Low-Beer, B. V. A., Friedell, H. L., and Lawrence, J. H. Metabolic studies on neoplasm of bone with aid of radioactive strontium. *Am. J. M. Sc.* 204:521-530, 1942.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 29151

PRESENTATION OF CASE

This fifty-two-year-old Russian-born housewife entered the hospital because of a generalized skin rash.

Six months prior to admission the patient developed a pruritic, burning, red rash on the palms of the hands, which became swollen. Her physician treated her for "poison ivy" without success. Several days later the eruption became dry and exfoliative and approximately two weeks later spread to the elbow and chest. The involved skin was first red and later turned brown and resembled a sunburn. The treatment was then changed to an ointment and a "wash." At that time she became increasingly fatigued, felt feverish and could no longer do housework. She was treated with pills that may have been sulfadiazine, which she took every four hours for two days without improvement. One month later the patient was sent to a community hospital for further study. While there, her temperature ranged from 99 to 103°F., but no chills occurred. A blood study apparently ruled out pernicious anemia, and a gastrointestinal series and barium enema were negative. After five days she was discharged unimproved. By that time the skin eruption had spread to the outside of the arms and to the knees, and was dry, gray and scaly. The patient remained in bed at home because of weakness and fever, for which her physician prescribed sulfadiazine, and one month later she entered another hospital. The gastrointestinal series and barium enema were repeated, and she was told that she had an irritable colon and insufficient acid in her stomach. Treatment consisted of a liver diet and hydrochloric acid without obvious effect. During the next month she had right-sided chest pain and a chronic cough developed, which produced small amounts of white, tenacious phlegm. Because her temperature was usually about 102.5°F. she was sent to a Boston diagnostic clinic.

There the skin of the entire abdomen was described as thickened and indurated, particularly over the chest. It was reddened with a generalized scaly, exfoliative rash, without ulceration, that produced white silvery scales, which were consistent with psoriasis. The palms, neck, face, trunk and legs were involved in that order of severity. The throat was congested and edematous. The tongue was fissured but the papillae seemed normal; no lead or bismuth line was noted. Fine moist rales were audible at the bases of both lungs; the heart was normal. The liver was felt one fingerbreadth below the costal margin. There was no abdominal tenderness or rigidity, and no masses were felt. The temperature was 103.4°F.

Laboratory studies revealed that the urine was acid in reaction, had a specific gravity of 1.008 and gave a + test for albumin and a green sugar test; the sediment contained an occasional hyaline cast, 40 to 50 white cells and a rare red cell and an occasional squamous epithelial cell per high-power field. The red-cell count was 3,390,000 with 68 per cent hemoglobin, and the white-cell count 9300 with 55 per cent polymorphonuclear neutrophils, 23 per cent band forms, 16 per cent lymphocytes and 6 per cent monocytes. The platelets were normal in number and appearance, and there was a rare microcyte and poikilocyte. The Wassermann and Hinton tests were negative. The blood sugar was 128 mg. per 100 cc., and two days later 112 mg. The sedimentation rate was greatly increased. Cultures of the urine and blood were negative.

An x-ray film of the chest disclosed calcified nodules in the right hilar region with markedly increased markings in the middle and lower thirds of the left lung, associated with a generalized increase throughout both lungs.

Sulfadiazine therapy was begun, using 1 gm. every four hours, but since the blood level eighteen hours later was 16.5 mg. per 100 cc., the dose was reduced to 1 gm. every six hours. The urine three days later was acid and showed a ++ test for albumin and a slightly green sugar test. The sediment contained 8 white cells, 4 red cells, occasional epithelial cells and many sulfadiazine crystals per high-power field. The blood sulfadiazine level was 14.8 mg. per 100 cc., the hemoglobin 64 per cent, and the white-cell count 4800. Because of the leukopenia and the sulfadiazine crystals in the urine, the drug was discontinued.

During treatment the temperature dropped to 98.8°F., and prior to discharge the urine had a fixed specific gravity varying between 1.012 and 1.013. The patient was transferred to this hospital for further study.

The patient's mother died of cancer. One brother died of heart trouble, and another broth-

er and a sister had heart trouble. The patient had had "flu" in 1918. Her last two children were not living—one died of "yellow jaundice" when eighteen days old, and the other was stillborn. An appendectomy and cholecystectomy were performed twelve years and six years prior to admission respectively. During the past year she had had irregular profuse menstrual periods associated with hot flashes.

Physical examination revealed an obese woman lying flat in bed groaning with each respiration and complaining of pain about the buttocks. The skin was generally dry and scaly and seemed atrophic, with loss of the subcutaneous fat in some places; there was a diffuse hair loss in the scalp. The face was ashen, particularly about the eyes. There were numerous thick silvery scales on the extensor surfaces of the arms and elbows, and the skin of the legs and knees was dry and covered with fine silvery scales. The palms of the hands and soles of the feet were rough, and the flexor surfaces of the fingers were fissured. There were red weeping areas on the chest and large denuded areas over each greater trochanter and over the buttocks. The tongue was very dry and covered with brownish tufts, and showed a slight coarse tremor. The cervical lymph nodes were slightly enlarged but not tender. The heart, lungs and abdomen were normal. A rectal examination was negative.

The blood pressure was 120 systolic, 88 diastolic. The temperature was 100°F., the pulse 120, and the respirations 25.

Examination of the blood revealed a red-cell count of 3,130,000 and a white-cell count of 10,500, with 59 per cent polymorphonuclear neutrophils, 11 per cent band forms, 21 per cent lymphocytes and 9 per cent monocytes. There was marked variation in the size and shape of the red cells, and a moderate hypochromia. The urine had a specific gravity of 1.008 and gave a + test for albumin; the sediment showed an occasional red cell and innumerable white cells. A phenolsulfonephthalein test was normal. The serum nonprotein nitrogen was 14 mg. per 100 cc., the sugar 108 mg., the protein 6.2 gm., the vitamin C 0.5 mg., the chloride 99.6 milliequiv. per liter, the sodium 140 milliequiv., the van den Bergh 1.2 mg. units direct (2.0 mg. indirect), and the prothrombin time 18 seconds (normal 18 seconds). A culture of the urine and a guaiac test on the stool were negative.

An x-ray film of the chest, taken with a portable machine, showed a high diaphragm on both sides, with linear areas of increased density in the left lower-lung field consistent with atelectasis.

The patient was treated with a high-vitamin, high-calorie diet with iron supplements. Vaseline was applied to the skin, and basic fuchsin to the decubitus ulcers. The lesions improved slightly, but one week after admission the temperature and pulse rose to 103.6°F. and 120 respectively. The cough increased, and signs of consolidation developed in the left lower lobe, associated with persistent rales. Two weeks later sulfadiazine therapy was instituted, 0.5 gm. every four hours for seven doses. Suddenly, three weeks after admission, fecal incontinence developed; these stools contained large amounts of dark, clotted blood, and the bleeding continued for the next twelve hours. On the same day a large ecchymosis appeared spontaneously on the left flank. The nonprotein nitrogen at that time was 22 mg. per 100 cc., the protein 4.0 gm., and the sulfadiazine level 4.1 mg. The urine was acid in reaction, had a specific gravity of 1.016 and gave a ++ test for bile; the sediment contained sulfadiazine crystals, a few cellular and granular casts and 3 white cells per high-power field. Despite blood transfusions and parenterally administered coramine, the systolic blood pressure fell to between 60 and 90 and the patient seemed to be in shock. Death occurred approximately seventeen hours after the onset of rectal bleeding.

Differential Diagnosis

Dr. Marian Ropes: We had better look at the x-ray films first.

Dr. Laurence Robbins: Both these films were made with a portable machine and are not particularly good. The diaphragm is elevated on both sides in the first film, and there are small localized areas that suggest atelectasis. The second film, taken several days later, shows slight increase in density and other areas that suggest atelectasis throughout the right lung field.

Dr. Ropes: I do not know what this patient had, but in any case with association of extensive skin lesions, marked constitutional symptoms, renal disease, leukopenia and fever, one strongly suspects that it represents one of the many varied clinical pictures of disseminated lupus erythematosus or, possibly, dermatomyositis.

One should consider the possibility of generalized infectious disease of nonspecific etiology, such as pyogenic infection, and also tuberculous infection. But the skin lesions, clinical course and laboratory findings all seem to me to rule out, or rather not to support, such diagnoses. The generalized nature of the disease, with suggestive evidence of vascular involvement in the kidneys, raises the possibility of periarteritis nodosa, but again, the skin lesions and the absence of signs of vascular involvement in the lungs, the central

nervous system, abdomen and so forth all tend to rule it out. The initial skin lesions might be found in a case of erythema multiforme exudativum, but the subsequent progression of the lesions, the fatal course and the leukocytosis are greatly against this diagnosis.

In attempting to differentiate the two conditions that seem to be the most likely explanation of the whole picture, the predominance of skin lesions with the absence of evidence of muscle involvement is strongly in favor of lupus. We are told nothing about the muscles, but this omission itself means, I should think, that there surely was no acute inflammatory involvement, probably no marked atrophy and no obvious contracture — all of which one would expect in a severe case of dermatomyositis. Also the absence of involvement of any of the small muscles — the pharyngeal, laryngeal and ocular muscles — and the evidence of renal disease are points against dermatomyositis, as is also the presence of pleurisy, which I interpret to be the cause of the right-sided chest pain.

The entire picture, although atypical, can be explained on the basis of disseminated lupus. This disease occurs most commonly in women, usually, to be sure, at a younger age. The distribution of the skin lesions, with involvement of the palms, face and neck, is typical. The nature of the skin lesions is far from typical, however, but I do not believe they fall beyond the many varied groups that in our present state of knowledge we think are due to this disease. The cervical node enlargement was minimal and may not have been significant (it is, of course, frequently observed in cases of lupus). The relative leukopenia, with a decrease in lymphocytes and an increase in young neutrophils is entirely consistent but not diagnostic. The atrophy of the skin with marked loss of hair is also entirely consistent but not diagnostic. If the patient had had any joint pains or had had more definite evidence of pericardial, endocardial or myocardial involvement this would have been additional evidence in favor of the disease. The absence of this evidence, however, does not rule out lupus. The original chest pain, which I interpret as having been due to pleurisy, is in favor of this diagnosis. The only possible indication of sensitivity to sunlight is obtained from the fact that the first skin lesions appeared after she had been in contact with poison ivy and probably had been in the sun. That, however, is weak circumstantial evidence.

The urinary findings indicate that renal disease was present. Whether this was due to one etiologic factor or to two or three, it is impossible to say. The changes increased consistently after each course of sulfadiazine, and the first report we have came after she had had one or two courses of sulfadiazine. It is conceivable that the kidney damage was due to the chemotherapy. On the other hand it is much more probable that it was associated with the disease, since renal damage is one of the most frequent complications of lupus. One might expect to find vascular lesions, perhaps of the so-called "wire-loop" type, in the kidneys. The terminal pneumonia is consistent with this disease, but also with any similar prolonged disease, and is in no way diagnostic.

The final episode of severe rectal bleeding is possibly connected in some way with the initial x-ray studies — the gastrointestinal series and barium enema. However, I am unable to find any reason for the two sets of x-ray studies. Also, I am unable to see why they gave the first two courses of sulfadiazine. In the absence of evidence of an infection that might be expected to respond to sulfadiazine, and in the presence of the possibility of lupus or of a similar skin lesion, sulfonamides are contraindicated because it is well known that they may cause severe and often fatal exacerbations of lupus. The final course of sulfadiazine was given in the presence of pneumonia. I still think that in the presence of lupus sulfonamides are contraindicated, but at least the indication is more apparent.

To return to the final episode — I had thought it was to be interpreted as bleeding from a severe ulcerative colitis. This does not fit in with the picture of lupus. We had one case that fell into this same general group of diseases, although Dr. Mallory was never able to include it pathologically in the group of disseminated lupus. Terminally, the patient had severe ulcerative colitis — not with massive hemorrhage but with definite bleeding. In the present case, other evidence of hemorrhage suggests that the rectal bleeding was associated with a generalized bleeding tendency. Whether this can be ascribed to liver involvement I do not know, but such a possibility is raised by the meager evidence of liver disease throughout the story. The slightly positive van den Bergh test and the palpable liver at one stage are suggestive, but the evidence is weak. I still believe that ulcerative colitis was the cause of the bleeding.

My diagnosis is disseminated lupus.

DR. ROBERT J. GLASER: I should like to ask Dr. Ropes if she considered mycosis fungoides.

DR. ROPES: I did consider it, and various other skin conditions, but I thought that it did not explain the whole picture so well as did the other diseases. The skin was the most typical part of

the whole picture and can be explained by a variety of conditions, but they do not explain the rest of the picture.

DR. AUSTIN BRUES: I saw this patient in consultation in the agonal stage and agreed with the surgeon that operation was not indicated and agreed with the house officer that transfusions should be given. By exclusion, and with considerable hesitation, I reached the diagnosis that Dr. Ropes has given.

DR. MALLORY: On reading the record, I found myself wondering whether anyone worried over the history of one jaundiced and one stillborn child to the point of suspecting that the patient was Rh negative. Apparently she was not because the transfusions were done without any reaction.

CLINICAL DIAGNOSIS

Disseminated lupus erythematosus?

DR. ROPES'S DIAGNOSIS

Disseminated lupus erythematosus.

ANATOMICAL DIAGNOSES

Acute hepatitis.
Purpura.
Gastrointestinal hemorrhage, massive.
Icterus, slight.
Neurofibroma of stomach.
Operative scar: cholecystectomy.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This is the kind of case that keeps the pathologist troubled because we have no more idea of the diagnosis after doing the autopsy than you have now, and perhaps a little less. I can only report the findings objectively.

The skin showed what is called an exfoliative dermatitis, which is certainly not a specific disease but a condition that can occur in the course of a variety of skin disorders. It occurs in psoriasis, in leukemia cutis, in mycosis fungoides and probably in lupus on occasion. I can only say that the sections show nothing to suggest psoriasis or mycosis, nothing on which a diagnosis of some underlying dermatitis can be based.

There was a severe and I think rather chronic pulmonary edema of both lower lobes. One small focus of organization was found, which suggested that there had been at least some degree of pneumonia in one of the lower lobes, but probably nothing recently acute. The heart was normal, as was the epicardium. There was a pleural effusion, but nothing that I could call a pleuritis. There were a few adhesions in the abdomen, but the patient had had a cholecystectomy. The gastrointestinal tract was filled with blood from top to bottom. In the stomach we found a circumscribed intramural tumor, which we thought was probably a leiomyoma or neurofibroma, but the mucosa over this tumor was intact, and I do not see how it could have been the source of the hemorrhage. On the other hand the mucosa of the intestine from top to bottom was hemorrhagic, and I think this was purpuric bleeding of massive proportions. The most strikingly abnormal organ was the liver, which was greatly enlarged, extremely fatty and markedly jaundiced. Microscopically, there is acute hepatic degeneration, and I assume that the purpuric tendency was secondary to liver insufficiency. At least we have nothing else on which to explain it because the bone marrow is normal and the kidneys, so far as we can make out, are completely normal. So we are left with a variety of pathological findings that correlate with none of the clinical observations and that to my mind point to no etiologic diagnosis.

DR. ROPES: Do you remember the other case with exfoliative skin lesions and liver involvement? I wondered if she had similar liver involvement.

DR. MALLORY: She had an extremely fatty liver, with slight cirrhosis. It did not show the acute degeneration found in this case. I think most of the liver change here must have been very acute, in fact terminal, because within a week of death there was a normal prothrombin time.

CASE 29152

PRESENTATION OF CASE

A sixty-seven-year-old school principal entered the hospital because of loss of weight and strength.

Nine months before entry the patient noted the onset of nausea with occasional vomiting after breakfast. At the same time he developed a "bronchial" cough productive of small amounts of whitish nonbloody sputum. This lasted two or three weeks, and two similar episodes occurred in the two following months. The paroxysms of cough were preceded by a tickling sensation in the throat, which he attributed to a large goiter that he had had for twenty-five years. There was no dysphagia. X-ray films taken by his physician were said to have shown four small gallstones and cloudiness at the apex of the right lung. He had been taking bile salts with some relief. During the four or five months before entry he became aware of progressive loss of strength and easy fatigue not relieved by rest. His appetite was poor, and he had lost thirty-eight pounds in weight during the previous

two months. Because of midafternoon fever of 99 to 100°F., he remained in bed for the two months prior to entry. Many specimens of sputum were negative for tubercle bacilli. Three weeks before admission the patient had his first attack of rapid pulse, the rate rising to 150, with associated headache and faintness. Since then he had three similar attacks, each beginning without warning and relieved by pressure on the eyeballs or carotid sinus.

He had had left-sided pleurisy twenty-five years previously, and pneumonia on the right and a suprapubic prostatectomy five years before entry. The family history was noncontributory.

Physical examination showed a well-developed but emaciated man with a dry and pale skin. There was a large, nodular, firm, but not stony-hard, tumor of the right lobe of the thyroid gland, which extended laterally beneath the sternocleidomastoid muscle and substernally. The trachea was deviated to the left. Examination of the heart and lungs was negative. The abdomen was slightly distended; in the right upper quadrant there was a definite sense of resistance and dullness but no well-defined border could be made out. The right kidney was movable, firm, nontender and neither enlarged nor displaced; the left was not palpable. Rectal examination was negative.

The blood pressure was 100 systolic, 45 diastolic. The temperature was 100°F., the pulse 90, and the respirations 20.

Examination of the blood showed a hemoglobin of 8.2 gm. and a white-cell count of 12,100 with 81 per cent polymorphonuclear neutrophils. The urine was cloudy and amber, had a specific gravity of 1.020 and gave a ++ test for albumin; the sediment contained a few red cells and many white cells. The stools were negative. A blood Hinton test was negative. The serum nonprotein nitrogen was 23 mg. per 100 cc. A sputum examination was negative for acid-fast bacilli.

An x-ray film of the chest showed numerous areas of calcification in the left midlung field and a 1.5-cm., slightly lobulated shadow of increased density with some calcification in the region of the right middle lobe. There was scarring in the right upper lobe. A mass at the base of the right neck with calcification in its walls displaced the trachea sharply to the left and extended slightly into the chest.

By x-ray the left kidney had a normal outline. The right kidney was enlarged and there appeared to be a definite bulge with some lobulation along the lateral surface. No stones were seen. An intravenous pyelogram showed prompt excretion of the dye on the left, which outlined normal urinary passages. The middle calyxes on the right were displaced medially and showed evidence of pressure defects without invasion. A retrograde pyelogram showed only partial filling of the right middle calyx.

Cystoscopy showed only a small amount of urine in the bladder. The flow of urine was extremely slight; at first the right ureter drained hazy urine followed by very bloody urine, and the left cloudy urine.

On the seventh day the white-cell count was 31,900. The temperature fluctuated between 99 and 101.2°F. Two days later an operation was performed.

Differential Diagnosis

Dr. Fletcher H. Colby: It seems to me that the significant history starts with the statement that the patient became aware of progressive loss of strength and easy fatigue not relieved by rest. He also had a low-grade midafternoon fever during that time. There were episodes of rapid pulse, which I imagine were attacks of paroxysmal tachycardia associated with the enlarged thyroid gland.

On physical examination the patient gave evidence of considerable loss of weight and strength. The mass in the neck was obvious, and from the history the patient had had this mass for twenty-five years. I assume that it probably was a colloid goiter. Although there is a possibility of malignant change, the fact that the patient had had this goiter for twenty-five years makes it seem improbable. The other essential points in the physical examination are the suspicion of a mass in the right upper quadrant, the pus in the urine and the confirmation by x-ray examination that there was a mass in the right upper quadrant. X-ray examination also showed an enlarged kidney, and this is certainly better evidence of enlargement of the kidney than physical examination, because we all know how large kidneys can be and yet be missed on palpation. The intravenous pyelogram suggests trouble in the right kidney. The left kidney was interpreted as normal. This suspicion of abnormality on the right seems to be confirmed by the cystoscopic examination, when a retrograde pyelogram made of the right kidney showed that the middle calyxes were displaced medially with a pressure defect and without evidence of invasion of the calyxes. So I believe that the important thing to consider in this patient is the right kidney. The evidence suggests that the mass was intrinsic in the kidney itself. The kidney outline was well shown by x-ray examination and appeared to be irregular, with a definite bulge. The retrograde pyelogram indicates that this mass in-

volved the middle portion of the kidney and displaced the middle calyx. So I think the diagnosis comes down to disease within the kidney itself. The possibility of perirenal infection seems to be eliminated. This mass on the right side, presumably the right kidney, was nontender, and one would expect perirenal infection to give tenderness.

Dr. Holmes, will you be kind enough to interpret the x-ray films?

DR. GEORGE W. HOLMES: I think I had better discuss the chest film first. The mass that is described is quite evident. It lies in the upper part of the anterior mediastinum in the region of the thyroid gland and contains calcium. So the only other things we have to think of are parathyroid tumor and a calcified tuberculous node. The position is very much against the latter. The findings in the lungs are more suggestive of tuberculosis than of anything else. There is one round shadow that might be a metastasis from a tumor.

DR. COLBY: That is the one with the fairly sharp edge?

DR. HOLMES: Yes; it is not quite so dense as one would expect it to be if it were old tuberculosis.

DR. COLBY: Calcification is described in that mass. Could it not be calcification somewhere else?

DR. HOLMES: It is not impossible for a tumor to show calcification. So I cannot state whether the shadow was due to tumor or to old tuberculosis. I do not see how one can connect it with the shadow in the neck.

DR. COLBY: The calcification in the neck is probably in the thyroid or parathyroid.

DR. HOLMES: I should think that was most likely because of the position. If the calcification was in a tuberculous node, the mass ought to lie alongside the trachea or up in the neck itself.

In the abdominal films there is a definitely enlarged right-kidney shadow. The lobulation is not so evident as one might expect from reading the notes, but I think it is present. The outline of the kidney is sharp, which is against an inflammatory lesion. In an inflammatory lesion, one usually does not visualize the kidney so well. The calyxes, although displaced, are not irregular, which again is against an inflammatory lesion. It apparently is deep in the substance of the kidney, so that it pushes the calyxes outward, and in all probability it is some sort of tumor. I doubt that a cyst would be in this position, and I shall be surprised if it turns out to be inflammatory. The density does not give a lead.

DR. COLBY: I think it is fair to say we come to the diagnosis of an intrinsic lesion of the right kidney. This could be either inflammatory or neoplastic.

What are the possibilities of an inflammatory lesion? First of all, a cortical abscess of the kidney should be considered. This is usually associated with preceding infection, which is possible in this patient, since he had had a low-grade fever for several months. However, he should have had backache and pain and he should have had tenderness. The pyelograms in such cases vary. My experience has been that with a cortical abscess there is a definite pressure defect, either of the kidney pelvis or, more often, of the calyxes themselves. The calyxes are usually compressed in a somewhat orderly fashion, and one does not see the irregular defects that are apt to be associated with tumor. So I do not believe this is a cortical abscess because of the lack of tenderness, the lack of pain, the lack of backache and the pyelographic evidence.

The only other inflammatory condition I can think of as a possibility is tuberculosis. The patient's age is against tuberculosis. Patients as old as this rarely have primary renal tuberculosis unless there is a definite past history of other lesions. That does not make it impossible. However, the patient apparently had had no bladder symptoms, and an irritated bladder is the most frequent symptom of renal tuberculosis. No ulceration or inflammatory change was described in the bladder on cystoscopic examination. Furthermore, the pyelogram was not consistent with tuberculosis. One would expect to find tuberculosis in more than one portion of the kidney, and as Dr. Holmes described the pyelogram, it does not suggest an inflammatory lesion.

So far as neoplasm is concerned, what is the possibility of metastatic malignant disease? The thyroid gland might have undergone malignant change, but I do not believe so, and I am going to discount that. Primary tuberculosis of the thyroid gland is rare, and if it occurs, is usually associated with miliary disease in general. Is that not true, Dr. Holmes?

DR. HOLMES: Yes.

DR. COLBY: At the Lakeville Hospital we have had only a few patients with tuberculosis of the thyroid gland.

The possibility of primary lung tumor that metastasized to the kidney should be mentioned. However, there is no real evidence that this patient had a primary carcinoma of the lung. In addition, the other systems give no lead to a pri-

mary tumor that might have metastasized to the kidney.

So we come down to the possibility of primary malignant tumor in this patient's right kidney. He had fever, weakness and loss of strength, and in our experience at this hospital these are evidence of malignant neoplastic disease somewhere. Although there is no convincing evidence of symptoms such as pain, hematuria and tumor, which are the three cardinal signs of renal tumor, these have long since been discarded as early indications of neoplasm. I cannot explain the fever except to say that it was evidence of infection. The well-marked anemia and the white-cell count of 31,000 after cystoscopic examination could have been due to the flaring up of an already present infection in the urinary tract. The kidney outline was suggestive of neoplasm, and the pyelogram indicated a tumor that involved the middle portion of the kidney. The area in the chest might have been a secondary deposit from a tumor of the kidney.

My diagnosis is a primary malignant tumor of the right kidney; and most of these tumors are renal-cell carcinomas.

Clinical Diagnosis

Carcinoma of kidney.

Dr. Colby's Diagnosis

Primary malignant tumor of right kidney.

Anatomical Diagnosis

Undifferentiated carcinoma of right kidney.

Pathological Discussion

Dr. Benjamin Castleman: At operation a large tumor (9 by 6 by 4 cm.) of the right kidney was found, which proved on section to involve most of the midportion of the kidney. The tumor was yellowish and necrotic, and microscopically shows an undifferentiated carcinoma, probably of embryonal origin. There was no invasion of the renal vein or pelvis, although the latter was displaced by the tumor.

Dr. Colby: Does anyone know anything about the nodule in the chest?

Dr. Castleman: No. The calcification in the neck might well have been a colloid goiter; many of them have some areas of calcification.

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CANCER CONTROL IN WARTIME

The urgency of caring for acute diseases and injuries in wartime naturally overshadows to some extent the importance of chronic diseases. Just as there has been an increase in the occurrence of pulmonary tuberculosis, there will undoubtedly be an increase in the number of advanced cases of malignant disease.

One of the unfortunate features of the shortage of physicians and nurses brought about by the war is that it becomes increasingly difficult to give the attention and study necessary for solving the difficult diagnostic problems not infrequently presented by cancer in its early stages. When, combined with this reduction in skilled personnel, there is a consequent reduction in the special facilities for caring for cancer patients, such as that now occurring at the Westfield and Pondville state hospitals for cancer, it becomes all the more important for the general public to be aware of the signs and symptoms of at least the commoner types of early cancer.

For several years the month of April has been designated as Cancer Month by the President. That custom is being continued this year. In spite of the excellent work that has been done in public education in the field of cancer in this state for the past years, it is well to remember that the point has not yet been reached at which one can be complacent with regard to the control of this disease.

An interesting study concerning the adequacy of the general public educational program in cancer control has been made recently in Connecticut.* Among 158 successive cancer patients admitted to the New Haven Hospital, over 80 per cent had delayed in seeking or following medical advice; 60 per cent of the patients did not regard their symptoms as "serious enough" to suggest cancer. Only 11 per cent came in without delay. About 25 per cent of the patients had read about cancer and only 2 patients had ever heard a lecture on cancer. Although, in general, the group could be regarded as poorly informed, 80 per cent of them believed that cancer was curable and 90 per cent realized that, once the presence of the cancer was established, treatment was urgent.

In connection with the activities in cancer education in Massachusetts, the Division of Adult Hygiene of the Department of Public Health is conducting a survey of a modified Gallup-poll type in Malden and has completed one in Lynn to determine what the general level of knowledge of cancer is among the population. It then contemplates carrying on educational work in this field and several years later re-surveying to determine the adequacy of such a procedure. Studies of this type will aid in evaluating the efficacy of educational cancer-control measures.

*Harms, C. R., Plaut, J. A., and Oughterson, A. W. Delay in the treatment of cancer. *J. A. M. A.* 121:335-338, 1943.

OBVIOUS MEDICAL CAUSES FOR DEFERMENT

MEDICAL Circular No. 3, issued by the National Headquarters of the Selective Service System,* deserves the attention of all physicians, especially those who are engaged in the preliminary physical examinations of men prior to induction into the armed forces. The circular lists both alphabetically and by systems the defects that are "manifestly disqualifying" and gives a brief outline of the procedure required for examinations by the local boards, whose purpose is to weed out the obviously unfit, thereby saving unnecessary travel expenses and also much time at the joint Army and Navy induction stations, where a man must (with rare exceptions) be examined completely by all the specialists even though he is rejected by one. In the past, failure on the part of the examining physicians to adhere strictly to Selective Service regulations has had the result that men with such gross defects as the loss of one leg or advanced tuberculosis were occasionally sent to induction stations. This need not be. The circular points out that there are three requisites to the success of his preliminary examination: enthusiastic acceptance of the program, complete familiarity with the *revised* regulations and strict adherence thereto.

The physicians who conduct the preliminary screening do so gratis. Their only recompense is the knowledge that they are performing an extremely important function; however, as the circular points out, they do have an excellent opportunity for increasing their ability to recognize truly disqualifying defects in the brief time at their disposal. That their work is appreciated by the medical officers of the Army and Navy cannot be overemphasized.

A half-hour study of this circular should do much to increase the effectiveness of the very important screening process daily taking place throughout the country.

*Preliminary physical examination. Medical Circular No. 3, issued by National Headquarters, Selective Service System, Washington, D. C. February 15, 1943.

MEDICAL EPONYM

TRAUBE'S SEMILUNAR SPACE

Ludwig Traube's (1818–1876) observations concerning this space are available only at second hand through a communication by one of his staff assistants, Dr. Fraentzel, who published contributions from the clinic of Privy Councillor Ludwig Traube entitled, "Bemerkungen über den halbmondförmigen Raum [Observations concerning the Semilunar Space]." This appeared in the *Berliner klinische Wochenschrift* (5:509–511, 1868). A portion of the translation follows:

> The fact that there is a region in the lowest part of the side of the thorax where the percussion note is tympanitic has long been recognized. Traube has made the first careful observations and investigations of this fact, the results of which may be summarized as follows:
>
> (*a*) The above-mentioned region of tympany has an approximately semilunar form, that is, it is bounded below by the costal margin and above by a curved line with its concavity directed downward.
>
> (*b*) This semilunar space begins anteriorly below the fifth or sixth costal cartilage and extends along the costal margin posteriorly to the anterior extremity of the ninth or tenth rib.
>
> (*c*) Its greatest width is three to three and a half inches [*Zoll*].
>
> (*d*) The note within this space, when the relation of the stomach and colon are normal, is distinguishable from the lung note above it not only by its tympanitic quality but also by its higher pitch.
>
> (*e*) With deep inspiration, as the lung descends, the semilunar space is considerably diminished, and this circumstance then serves as evidence of normal mobility of the lung margin.
>
> (*f*) A significant enlargement or widening, usually associated with immobility of the lower margin of the left lung, is one of the most important signs of retraction of the lung.
>
> (*g*) In the presence of pleuritic exudate, the semilunar space may completely disappear, and the beginning of resorption may be first indicated by its reappearance, and its disappearance at times may be most clearly demonstrated by the widening of the space.
>
> (*h*) In the presence of pneumonic infiltration of the whole left lower lobe, the semilunar space either remains intact or is only slightly narrowed.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON INDUSTRIAL HEALTH

Some changes in the timing of the program on Industrial Health to be held at the Harvard Club in Boston on April 24 have been necessary. The corrected program is as follows:

9:30 Methods Used in Establishing a Diagnosis of Industrial Poisoning. Dr. Joseph C. Aub.

10:00 The Late Effects of Craniocerebral Trauma: A consideration of the criteria necessary to evaluate the possible causes. Dr. Donald Munro.

10:30 Medical Causes for Rejection in Selective Service. Lt. Colonel Lewis S. McQuade.
Neuropsychiatric Causes for Rejection in Selective Service. Dr. Harry C. Solomon.

11:15 Medical Aspects of Absenteeism in Industry. Dr. Louis R. Daniels.

12:30 Luncheon (Guest speaker: Dr. Alice Hamilton).

2:15 Present Status of Relation of Heart Disease to Industry. Dr. Paul D. White.

2:45 The Problems of Women in Industry. Dr. Thomas L. Shipman.

3:30 Epidemic Keratoconjunctivitis. Dr. Irving R. Tabershaw.

4:00 Opportunities for the Prevention and the Treatment of Diabetes in Industry. Dr. Elliott P. Joslin.
The Treatment of Trauma in Diabetic Employees. Dr. Leland S. McKittrick.
Industrial Hazards for Diabetic Employees. Dr. William A. Bishop.

Dwight O'Hara, *Chairman*

SECRETARY'S OFFICE

The following letter deserves close scrutiny by all members of the Massachusetts Medical Society.

Michael A. Tighe, *Secretary*

* * *

City of Boston
Veterans' Graves Registration

March 25, 1943

Dear Dr. Tighe:

Chapter 46, Section 10, of the General Laws calls for the physician, as indicated on the face of the standard certificate of death in red letters, to furnish information concerning military service, if any, on the part of the deceased.

In several certificates that have recently come into the Registry with the word "No," we have found that the deceased was a veteran, owing to the request of some party for a certified copy of the certificate.

We ask that your membership be advised of the above matter.

May I express my appreciation of your help and courtesy in the past.

Yours very sincerely,
F. W. Foss, *Supervisor*

Veterans' Graves Registration
City of Boston

DEATHS

BYRNE — Charles A. Byrne, M.D., of Hatfield, died April 3. He was in his eighty-first year.

Dr. Byrne received his degree from Long Island College of Medicine in 1894. He was a member of the Massachusetts Medical Society and the American Medical Association.

DENNISON — Archibald S. Dennison, M.D., of Lynn, died January 22. He was in his seventy-fourth year.

Dr. Dennison received his degree from the Bellevue Hospital Medical College, New York, in 1896. He was a member of the Massachusetts Medical Society, the American Medical Association and the American College of Physicians.

DWYER — Philip R. Dwyer, M.D., of Salem, died February 28. He was in his forty-ninth year.

Dr. Dwyer received his degree from Harvard Medical School in 1920. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and a daughter survive him.

GATES — Ernest A. Gates, M.D., of Springfield, died January 4. He was in his seventy-second year.

Dr. Gates received his degree from the Dartmouth Medical School, Hanover, New Hampshire, in 1895. He was a member of the Massachusetts Medical Society and the American Medical Association.

HENDERSON — Charles R. Henderson, M.D., of Reading, died March 31. He was in his seventy-sixth year.

Born in Hertford, England, he received his degree from Boston University School of Medicine in 1889. He was school physician in Reading for twenty years. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive him.

HOLMES — May S. Holmes, M.D., of Orleans, died April 4. She was in her seventy-third year.

Born in Lee, she received her degree from the Woman's Medical College of the New York Infirmary for Women and Children in 1895. She was formerly superintendent of the Belmont Hospital, Worcester. She was a member of the Massachusetts Medical Society and the American Medical Association.

LOWELL — William H. Lowell, M.D., of Winchester, died March 31. He was in his sixty-eighth year.

Born in Halifax, N. S., he received his degree from the Harvard Medical School in 1902. He was for many years a member of the staff of the Massachusetts Eye and Ear Infirmary and was consulting surgeon to the Massachusetts General Hospital, to the Lawrence Memorial Hospital in Medford and to the Lawrence General Hospital. He was on the board of examiners of the American Board of Ophthalmology.

Dr. Lowell was a member of the Massachusetts Medical Society, the American Medical Association, the American Academy of Ophthalmology and Oto-Laryngology, the New England Ophthalmological Society and the Harvard Club of Boston.

His widow, a son and a daughter survive him.

WAR ACTIVITIES

INDUSTRIAL MEDICINE

Control and Treatment of Nitrous-Fume Poisoning

A conference on nitrous-fume poisoning was held in Cincinnati, Ohio, on January 28, 1943. The literature on poisoning by nitrous fumes and case histories of recent fatal and nonfatal cases of poisoning were reviewed. The suggested engineering control measures were ventilation, adequate exits and proper storage of materials likely to cause nitrous-fume exposures.

Several medical control measures were suggested:

(1) Pre-employment examinations should include x-ray films of the chest and the exclusion from employment persons with certain upper respiratory conditions, asthma, reactivated tuberculosis and diseases of the heart.

(2) Any exposure should be reported promptly, and the worker should be referred to the hospital for an evaluation of exposure.

(3) Any workers showing evidence of burning of the throat or chest, epistaxis, lassitude, pallor, cyanosis and abnormal breathing should have absolute bed rest for twenty-four hours as a minimal period of observation (distressing symptoms may show up as long as seventy-two hours after exposure). During the observation period the patient should be kept warm, supplied with oxygen if necessary, given a liquid diet and have his blood pressure and pulse taken at regular intervals and recorded. The blood picture should also be studied periodically, particularly as regards the red-cell count and hemoglobin and methemoglobin determinations.

If definite evidence is obtained that pulmonary edema is developing:

(1) Bleed the patient (500–600 cc.).

(2) Use plasma to combat the hemoconcentration.

(3) Administer oxygen continuously (administration under pressure may be advisable).

(4) Do not give morphine; if sedation is necessary, Allonal or luminal should be used.

(5) Use of cardiac stimulants should be discouraged.

(6) As this is an uncompensated alkalosis, soda is contraindicated.

(7) Give concentrated glucose intravenously.

(8) Mercury diuretics may be tried.

(9) Adrenocortical hormones may be tried.

(10) The most satisfactory treatment is prevention.

—Reprinted from *Industrial Hygiene*, a bulletin issued monthly by the Division of Industrial Hygiene, United States Public Health Service.

MISCELLANY

GRADUATION AT TUFTS

A total of 94 men and women were graduated by the Tufts College Medical School at convocation ceremonies held jointly with Tufts College Dental School on Sunday afternoon, March 28, in the Cousens Gymnasium on the Medford campus. Three of the ten medical students graduating with honors are residents of Metropolitan Boston: Elliott Bresnick, of Brookline; Lawrence F. Cozza, of Somerville; and George L. Cushman, of Medford. In addition to being the first convocation of degrees held since the war-accelerated training program was adopted a year ago, the exercises were the first that the two schools have held separately from the other schools of Tufts College.

Honorary degrees were awarded to three physicians. The degree of Doctor of Laws was conferred on Dr. Lewis H. Weed, professor of anatomy at Johns Hopkins University School of Medicine, and chairman of the Division of Medical Sciences, National Research Council, who delivered the convocation address, "War Research in Medicine and Dentistry." The degree of Doctor of Science was awarded to two alumni of Tufts College Medical School: Commander A. Warren Stearns, U.S.N.R., dean of the school, who is now in active service, and Dr. Frank R. Ober. Dr. Lee S. McCollester, chaplain emeritus of Tufts College, gave the prayer and benediction.

REPORT OF MEETING

GREATER BOSTON MEDICAL SOCIETY

A regular meeting of the Greater Boston Medical Society was held at the Beth Israel Hospital on November 11, 1942, with Dr. Hyman Green presiding. Dr. Joseph C. Aub spoke on the topic "The Present Status of Hormone Therapy," making special reference to the role of testosterone and diethylstilbestrol.

It was emphasized that the mode of action of many of the hormone products is not understood, and that what is known is based largely on evidence gleaned from urinary assays. But a low assay may be interpreted in a variety of ways, for instance as a greater breakdown in the body before secretion, or as a diminished secretion.

Testosterone was isolated in 1934 and crystallized the following year. It has been found to be ten to twenty-five times more potent than other androgenic substances. The effect of this, like that of other hormones, is greater when there is a definite lack in a patient. The best index of activity is the effect on children. This substance causes a marked increase in the size of the penis or clitoris, including as well as of the prostate and the seminal vesicles in boys, and a development of all secondary sex characteristics. The results are dramatic in the eunuch, in whom the deficiency is outspoken. Such patients should receive 25 mg. intramuscularly three times a week or 10 to 20 mg. of the methyl salt daily by mouth. The deepening of the voice that may occur sometimes alarms girls, but is usually a reversible change, which can be rectified by withdrawal of the drug. There may also be hirsutism with male distribution, as well as an increase in musculature and a swing toward a male type of habitus. All these effects are apparently greater following the intramuscular use of the hormone. In those lacking the hormone, such as eunuchs, there is generally a feeling of well-being, with aggressiveness and increased libido. It should be noted that the use of testosterone also affects other internal organs, as evidenced by an increase in size of the kidneys and so forth. In all these hormonal appraisals, the balance between the male and female factor is probably more significant than the absolute amount of either. For example, those with Fröhlich's syndrome may excrete large amounts of ketosterones and have high estrogen values as well.

Testosterone has a definite effect on skeletal growth and epiphyseal closure. There is great stimulus to growth, especially in undersized children, and at the moment, it is the best available material for this purpose. The increase in secondary sex characteristics limits the amount of therapy that can be given. The two important factors are growth and maturation. No stimulus is of much value if it increases the closure of epiphyses at the same or a faster rate than it stimulates growth. But it is thought that testosterone, unlike desoxycorticosterone, increases the bone age little if any and is therefore superior as a therapeutic agent in stunted growth of endocrine etiology. Oral methyl testosterone is satisfactory for this purpose in daily doses of 10 to 20 mg. The appearance of secondary signs is less of a problem, but one should watch for evidence of hirsutism and change of voice. Although the hair usually disappears with withdrawal, the change of voice is often permanent.

Knowledge of the growth mechanism has been obtained from a study of deer antlers. In this animal there is only one cycle, the testes being quiescent from December to June, followed by activity associated with tremendous

antler growth. The rate of growth far outstrips any known tumor, and there is associated growth of all other sex characteristics. Although the local phosphatase values are high at the antler tip, there is no change in the serum phosphorus, calcium or phosphatase, unlike cases of osteogenic sarcoma. The antlers start their growth at least one month before any change in the testes, and growth stops when the testes atrophy. Castration when the antlers are well developed causes them to drop off soon; whereas the same procedure at an early period results in a slow, gradual increase in their size over the entire year. The latter never drop off. The impetus probably arises in the anterior portion of the pituitary gland, as evidenced by growth of the antlers before the testes. No change in the thyroid or adrenal gland has been noted at any time.

The use of testosterone in women has led to many controversies. The importance of the ketosteroid-estrogen relation was again stressed. There seems to be some effect on libido, whereas there is definite improvement in certain cases of endometriosis and questionable benefit in patients with uterine fibroids. In normal women, menstruation may be suppressed for several months if enough is given. This is probably a secondary effect through the pituitary gland. This disturbs the ovarian cycle. One of the most practical uses of the drug is in reducing mastodynia and premenstrual stress. At the menopause, it is apparently as effective as the estrogens, although the mechanism has as yet not been established. The pruritus and eczema of this trying period also seem to be benefited.

Diethylstilbestrol, although it is chemically not a true estrogen, has the same physiologic effects. However, it is also a more potent carcinogenic agent and should therefore be used with caution. It is not a substitute for the estrogens but is interchangeable with them, at least at the menopause. The disadvantages are occasional nausea and skin lesions, such as pruritus and a macular rash. A few patients exhibit evidence of allergy although they have never before had the drug. There have been no serious sequelae. A good indication of sufficient hormone is the onset of mammary enlargement in either sex, with some discomfort and tingling. This may even occur in children in whom the drug is being used for the treatment of vulvovaginitis. The breast enlargement seems to be ductile and periductile rather than acinar. The drug is certainly a satisfactory hormone, and many of the objections to it seem unfounded. Doses of 0.5 to 1.0 mg. daily by mouth seem innocuous from the standpoint of carcinogenesis. It is much cheaper than the estrogens. End-result studies are not yet available, however.

The anterior portion of the pituitary gland is probably the stimulator of the above-mentioned organs, and its substance would therefore be the drug of choice. But there are as yet no potent nor proved preparations from this master gland. Therefore, treatment is now of the substitute variety. One of the main faults with such therapy is that the secondary sex characteristics are stimulated without any effect on the sex organs or their secretions. The latter may even be decreased.

The discussion was started by Dr. Harry B. Friedgood. Testosterone treatment of youngsters should still be confined to physicians who are acquainted with the physiology of the substance, since there may be untoward effects. There is no question that this substance does cause descent of the testicle and bone growth. Testosterone in the management of eunuchs is remarkable: it improves their emotional stability and decreases their tendency for infections of all sorts. It is believed that oral methyl testosterone is as satisfactory as testosterone from the point of results and is somewhat safer. There should be some hesitation in the use of this hormone in girls and women because of its ill-effects. Hypertrophy of the clitoris may remain, as well as a permanent change of voice, and hirsutism often recedes only slowly. If employed the patient should be followed with vaginal smears and all manifestations should be closely checked.

Dr. Friedgood is reticent about using diethylstilbestrol because of its lack of chemical similarity to the estrogens. Furthermore, the short duration of untoward symptoms does not rule out a toxic effect. The end results on this score are still to be recorded, and there have been reports of toxic changes of the liver and kidneys.

Dr. Samuel Gargill emphasized the efficacy of testosterone as a substitute for the estrogens in certain conditions. He has been impressed with the superior qualities of the methyl derivative for growth stimulus and also for the control of functional uterine bleeding. Diethylstilbestrol has been used for four years with few reactions. It has been especially effective at the menopause. Ethanol estradiol competes in cheapness and is good in small doses, but there are still some toxic manifestations.

Dr. Henry Finkel spoke about the efficacy of progesterone in the treatment of habitual or threatened abortion. This procedure is based on the theory that there is in such women a deficiency of this hormone, which is thought to be responsible for proper implantation of the ovum and for a decrease of uterine contractions. Often in abortions the fetus has been dead for several weeks, and in such cases there is actual harm in prescribing this hormone, because of the danger of malignant degeneration in a retained fetus. Therefore, progesterone should be administered post conception in suspected cases, and even then it will be of avail only if there is a progesterone deficiency and all other conditions are normal.

In conclusion, Dr. Aub warned against the dangers inherent in these preparations, which will be enhanced with further purification of the hormones. All those planning to employ them should be acquainted with the proper dosage and the side effects.

(Notices on page xii)

CONSIDERATION OF IRRITATION OF THE NOSE AND THROAT BECOMES INCREASINGLY IMPORTANT

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* *Laryngoscope, Feb. 1935, Vol. XLV, No. 2, 149-154*
Laryngoscope, Jan. 1937, Vol. XLVII, No. 1, 58-60

NOTICES

BOSTON ORTHOPAEDIC CLUB AND NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

There will be a combined meeting of the Boston Orthopaedic Club and the New England Society of Physical Medicine at the Boston Medical Library on Monday evening, April 26, at 8 p.m.

PROGRAM

Recent Advances in the Concept and Therapy in Poliomyelitis. Dr. Herman Kabat, assistant surgeon, United States Public Health Service, and member, Division of Physical Therapy, University of Minnesota Medical School.

Recent Experiences in the Treatment of Poliomyelitis. Dr. Robert L. Bennett, director of physical medicine, Georgia War Springs Foundation.

Discussion by Drs. William T. Green and Paul L. Norton.

All members of the medical profession are cordially invited to attend.

BOSTON HEALTH LEAGUE

The annual meeting of the Boston Health League will be held at Perkins Hall, Women's Educational and Industrial Union, 264 Boylston Street, Boston, on Thursday, April 22, at 12:30 p. m.

PROGRAM

Proposed Extension of Medical Benefits under Social Security. Mr. I. S. Falk, director of Bureau of Research and Statistics, Social Security Board, Washington, D. C.

Payment for Medical Care for the Indigent under the Proposed Green and Coffee Bills. Dr. B. W. Mandelstam.

The charge for luncheon will be 75 cents. Reservations, sent to the Boston Health League, 261 Franklin Street, Boston, should be made by Tuesday, April 20.

EVANGELINE BOOTH MATERNITY HOSPITAL

A meeting, open to physicians, will be held at the Evangeline Booth Maternity Hospital, 202 West Newton Street, Boston, on Wednesday, April 21, at 8:15 p.m. Dr. Boris E. Greenberg will speak on the subject, "Spermatozoa and Low Fertility." The talk will be illustrated by lantern slides followed by motion pictures presenting the life of the spermatozoa.

BOSTON MEDICAL HISTORY CLUB

There will be a meeting of the Boston Medical History Club at the Boston Medical Library, 8 Fenway, on Monday, April 26, at 8 p.m. Dr. Dwight O'Hara will speak on the subject, "Horatio Adams (1801–1866), a Doctor in Waltham."

All interested persons are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, APRIL 18

TUESDAY, APRIL 20

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. The Medical Aspects of Alcoholism. Dr. Robert Fleming. South End Medical Club. Headquarters, Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

2:00–4:00 p.m. Myasthenia Gravis Clinic. Out Patient Department, Massachusetts General Hospital.

WEDNESDAY, APRIL 21

*9:00–10:00 a.m. Statistics in the Determination of the L. D. 50 Point in Bio-assay. Dr. E. B. Wilson. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

*8:15 p.m. Spermatozoa and Low Fertility. Dr. Boris E. Greenberg. Evangeline Booth Maternity Hospital, 202 West Newton Street, Boston.

THURSDAY, APRIL 22

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

12:30 p.m. Boston Health League. Women's Educational and Industrial Union, 264 Boylston Street, Boston.

FRIDAY, APRIL 23

*9:00–10:00 a.m. Comparative Action of Glycosides on the Mammalian Heart. Dr. Gordon Moe. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, APRIL 24

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

*Open to the medical profession.

APRIL 26. Boston Medical History Club. Notice elsewhere on this page.

APRIL 26. Boston Orthopaedic Club and New England Society of Physical Medicine. Notice elsewhere on this page.

APRIL 27. Cutter Lecture. Page x, issue of April 8.

MAY 19–25. American Board of Obstetrics and Gynecology. Page xii, issue of March 4.

MAY 24–27. War Conference. Page ix, issue of March 25.

MAY 25 and 26. Massachusetts Medical Society. Hotel Statler, Boston.

JUNE 4 and 5. American Board of Ophthalmology. Page xii, issue of March 4.

DISTRICT SOCIETIES

BRISTOL SOUTH
MAY 6. New Bedford.

ESSEX NORTH
MAY 5.

ESSEX SOUTH
MAY 5. Salem Country Club.

FRANKLIN
MAY 11. Annual meeting.
Meetings are held at 11:00 a.m. at the Franklin County Hospital, Greenfield.

HAMPSHIRE
MAY 5.

MIDDLESEX EAST
MAY 5. Bear Hill Golf Club, Stoneham, 6:30 p.m.

MIDDLESEX NORTH
APRIL 28.
JULY 28.

PLYMOUTH
MAY 20. Lakeville.

WORCESTER
MAY 12. Annual meeting.

WORCESTER NORTH
APRIL 28.
JULY 28.

(Books Received on page xv)

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Alcohol Explored. By Howard W. Haggard, M.D.; and E. M. Jellinek, M.D. 8°, cloth, 297 pp., with 10 illustrations and 20 tables. Garden City, New York: Doubleday, Doran and Company, Incorporated, 1942. $2.75.

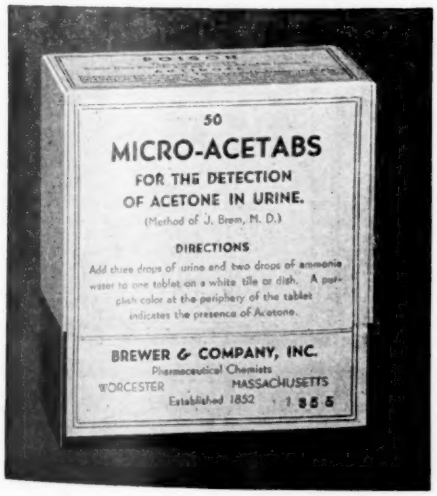
This popular book on alcohol deals with the subject in its physiologic, social and economic aspects. The subject is not approached from the point of view of the reformer but is discussed by two men who are authorities in their field. Dr. Haggard is director of the Laboratory of Applied Physiology of Yale University and Dr. Jellinek, also of Yale, is vice-chairman of the Scientific Committee of the Research Council on Problems of Alcohol. Both authors are editors of the *Quarterly Journal of Studies on Alcohol.*

Fractures. By Paul B. Magnuson, M.D., associate professor of surgery, Northwestern University Medical School, and attending surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago. Fourth edition. 8°, cloth, 511 pp., with 317 illustrations. Philadelphia: J. B. Lippincott Company, $5.50.

This is the fourth edition of a standard work on fractures. The only additional material added to this edition has to do for the most part with first aid, transportation and early treatment of compound fractures during the present war. The suggestions along these lines represent the consensus of the Committee on Orthopedic Surgery of the National Research Council, as constituted at the time of the publication of this edition. It is urged as in the past that each fracture be considered as an individual case and that treatment be based on the knowledge of the physiology and anatomy of the parts involved, according to the theory that it is an injury to the body as a whole, not to just one part of the body. In this connection, the treatment of wounds, especially of wounds in compound fractures, the use of sulfatherapy and the treatment of shock are also included.

Food Charts. Prepared by a joint committee of the Council on Foods and Nutrition Board, National Research Council. Used in connection with a scientific exhibit at a meeting of the American Medical Association. 8°, paper, 20 pp., with 8 charts and 2 tables. Chicago: American Medical Association. 10 cents.

This little book provides considerable factual information about foods as sources of the dietary essentials. The eight charts show the contributions that individual foods make with respect to the needs for protein, calcium, iron, vitamin A, thiamine, riboflavin, niacin and ascorbic acid. A feature of these graphic presentations is that the values are presented in terms of the proportion of the daily requirements which are supplied by typical servings of each food. The requirements selected are daily allowances recommended by the Council on Foods and Nutrition of the National Research Council.



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